Plasma cell disorders

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The online version of this chapter contains an educational multimedia component on the basics of gammopathy testing.

Introduction

Plasma cell (PC) disorders—sometimes still collectively referred to by the older term *dyscrasias*—are clonal neoplasms of PCs resulting in a spectrum of clinical conditions, ranging from the very early, asymptomatic, states of minimal clonal expansion to symptomatic disease states with associated end-organ damage. When the clonal expansion reaches a critical level there is compromise of organ function and patients are said to have myeloma-defining events. The most common characteristics include bone destruction, anemia, and renal failure.

The symptomatic phases of the plasma cell neoplasms (ie, multiple myeloma [MM]) are more commonly seen in patients in the sixth and seventh decade of age, although PC disorders have been identified in patients of all ages. The earliest state (and state of highest prevalence) that is clinically identifiable is called the monoclonal gammopathy of undetermined significance (MGUS). By definition, this stage is asymptomatic, although in some rare cases the nature of the monoclonal proteins can lead to paraneoplastic-like complications (monoclonal gammopathy of renal significance [MGRS], amyloidosis, and capillary leak syndrome, among others). The vast majority of patients with MGUS enjoy a normal life span with no clinical consequence, other than the distress of the new diagnosis. A small fraction of patients progress to MM every year, with the risk of progression never disappearing. Rigorous epidemiologic studies conducted in Olmsted County, Minnesota, have shown variability in this risk, a large fraction of which is stochastic (ie, the more cells, the higher the risk of progression, or extreme variation in the free light-chain [FLC] assay) or biological nature (eg, immunoglobulin A [IgA] more likely to progress than IgG or higher risk of progression with high-risk genetics). It is of paramount importance to differentiate IgM MGUS from non-IgM MGUS because

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Off-label drug use: Melphalan has no FDA approval for the treatment of myeloma. Venetoclax is not approved for the treatment of myeloma. Proteasome inhibitors are not approved for maintenance therapy for myeloma. The combination of carfilzomib with alkylators is not FDA approved. Isatuximab is not approved in combination with immunomodulatory drugs for myeloma."

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the former is rarely, if ever, associated with progression to MM, and, for all practical purposes, these 2 entities should be considered separate pathologies. In the ensuing sections, we cover the various PC disorders, including diagnostic criteria and individual treatment approaches.

Normal plasma cell development

Development of a fully functional antibody-secreting PC from a B lymphocyte is a multistep process that is initially independent of antigen exposure, followed by a late antigen-driven phase. Normal differentiation from early B cells to PCs is characterized by 3 B cell–specific DNA remodeling mechanisms involving the Ig genes:VDJ rearrangement, somatic hypermutation, and class-switch recombination. This last step is what creates a fundamental distinction between IgM and non-IgM neoplasms, much like what is observed with primary versus secondary immune response. It is precisely at the germinal center that somatic hypermutation and class switching occur and where it is now believed that PC neoplasms originate. An extremely rare exception is the diagnosis of IgM MM, which is a rarity.

Once successful light-chain rearrangement occurs, the cell expresses a complete Ig molecule on its surface (typically IgM or IgD), which identifies it as a mature B cell. Next, antigen-dependent development begins when a naïve mature B cell in a germinal center recognizes an antigen with its membrane-bound surface antibody, which triggers 2 separate processes: somatic hypermutation and class-switch. Somatic hypermutation is a process by which cells introduce mutations into the variable-region genes, providing a repertoire of competent cells with varying degree of affinity for the antigen. Class switching involves changing the heavy chain that is expressed to transform late B cells from production of IgM and IgD to production of IgG, IgA, or IgE. This mutational process makes PCs live a perilous life, and it is now believed that genetic defects, arising from mistakes in this usually unforgiving process, are what causes MM. Finally, the antigen-exposed hypermutated and class-switched PC migrates to the bone marrow, where it interacts with marrow stromal cells before finally differentiating into a long-lived antibody-producing PC. In the human body about 70% of plasma cells produce IgA and live in mucosal tissues (IgA MM tends to be more aggressive), but about two thirds of myeloma cases arise from IgG-producing cells.

Detection of plasma cell disorders

The diagnosis of a PC disorder depends at which stage the disease is detected. MM is usually detected because of symptomatology, while MGUS detection is usually a result of other medical investigation. The canonical hallmark is the detection of a monoclonal protein in the serum (or urine), and, less commonly, initial detection of monoclonal PCs in the bone marrow, peripheral blood, or plasmacytomas (Figure 25-1). Various laboratory tests can be used to detect these monoclonal proteins, including serum protein electrophoresis (SPEP), urine equivalent, immunofixation (IFE), or serum free light-chain assay.

Protein electrophoresis involves charge- and mass-based separation of proteins on a gel, which allows detection of the presence of a monoclonal protein because of the characteristic narrow spikes in the γ and sometimes β region (more commonly for IgA monoclonal proteins). This test has relatively low sensitivity (~0.2 g/dL) and misses small monoclonal proteins and monoclonal light chain. Immunofixation is a more sensitive study needed only to characterize the nature of monoclonal proteins (type) or to quantify at a lower level than the SPEP as required by the new disease response criteria. IFE uses antibodies directed against each of the heavy chains and the κ and λ light chains. This allows identification of the type of monoclonal protein in terms of heavy-chain and light-chain isotypes, as well as detection of small amounts of monoclonal protein otherwise not detected on protein electrophoresis. A novel technique used to detect and monitoring monoclonal proteins is a mass spectroscopy approach. This technique is highly sensitive and can differentiate the original monoclonal protein from therapeutic antibodies. It can also detect posttranslational modifications and glycosylation that seem to be associated with a higher likelihood of amyloid deposition.

In a small proportion of patients, both the SPEP and IFE can be negative because the PCs may secrete only light chains (κ- or λ-free light chains). The serum FLC assay allows quantitation of monoclonal FLCs circulating (unbound to the heavy chain) by virtue of the assay's reactivity against exposed FLC epitopes that are normally hidden when light chains are bound to the heavy chain. The FLC assay signals the presence of a clonal process when the ratio between κ- and λ-FLC is skewed from the normal range, and, more importantly, the FLC assay also allows quantitation of the clonal light chain with high sensitivity at very low serum concentrations (eg, an upper limit of normal value of 2 mg/dL). With these 3 tests, more than 98% of patients with PC disorders can be demonstrated to have a monoclonal protein, leaving behind a very small minority of patients who are truly nonsecretory in that they do not produce or secrete any monoclonal protein. While debatable, it is less clear how 24-hour urine collection can be important in the future for measuring monoclonal proteins, given that most of these proteins are only

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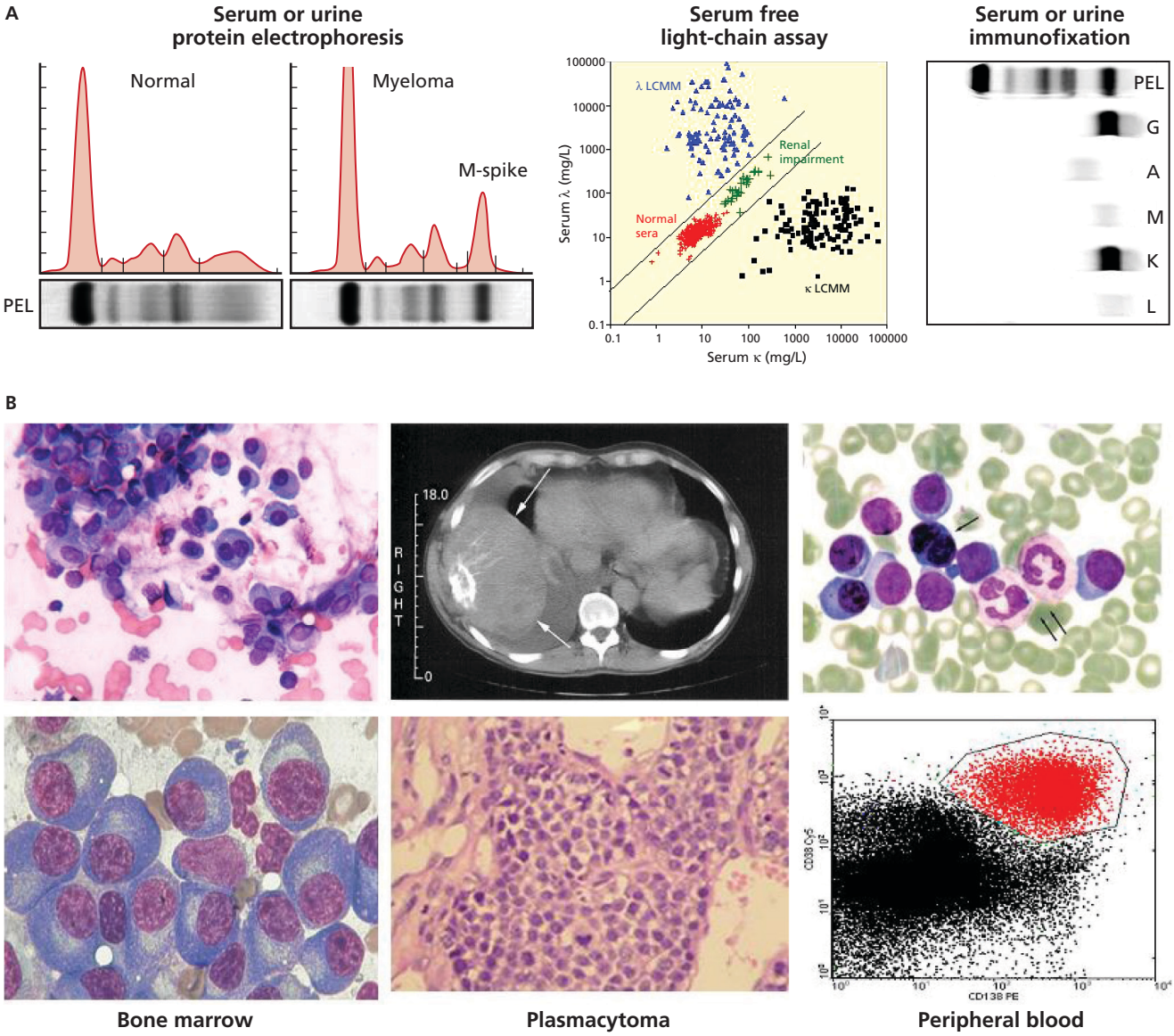

Figure 25-1 Diagnostic tests for monoclonal protein and PCs.

light chains; heavy chains are not readily filtered, and, with the advent of the serum free light chain (sFLC), these can be measured in the serum. A novel assay, the Heavy Lite assay, can specifically measure combinations of heavy and light chains in a way that is unique to the specific MM case. Most MM experts use only this assay in the case of IgA MM with very-low-concentration monoclonal proteins.

The next step in the evaluation is performing a bone marrow biopsy and aspirate to ascertain the origin of these monoclonal proteins. In most cases monoclonal PCs are detected, although in some cases the percentage of cells is discordant with what would be expected by the serum concentrations of these monoclonal proteins. While the normal fraction of PCs in the bone marrow is between 1% and 2%, most clinicians consider a plasmacytosis <5% as normal, given the sampling variation. Clinicians should consider the readout of the highest percentage of PC content, whether it is in the biopsy or the aspirate. Because of issues related to hemodilution of aspirates obtained in last order, it is not unusual to see very low percentage values of PC in third- tube aspirates, usually those sent for flow cytometry. In addition, adherence of plasma cells to bone marrow spicules and loss of surface expression of CD138 and CD38 due to cell processing, as well as hemodilution, have been suggested as mechanisms responsible for

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low PC counts when using flow cytometry. The bone marrow can vary anywhere from normal looking to near total replacement by clonal PCs. Unfortunately, the marrow involvement in MM can be patchy, resulting in sampling variation during biopsy. Circulating PCs are rare and mostly detected by flow cytometry. If their absolute number is high, then a diagnosis of plasma cell leukemia (PCL) should be considered. Finally, a small proportion of patients present with soft tissue masses (plasmacytomas), with or without associated bony destruction; biopsy of plasmacytomas shows sheets of monoclonal PCs.

Disease definitions

The spectrum of PC disorders consists of MGUS, smoldering (asymptomatic) MM (SMM), MM, and plasmacytoma (which can be solitary or multiple and also bony or extramedullary). Other associated conditions include light-chain (AL) amyloidosis, monoclonal Ig deposition disease, and POEMS syndrome (ie, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) (Table 25-1). In addition, several conditions have been described in the context of a monoclonal protein or monoclonal PCs but are relatively rare; their pathophysiology is not well understood (Table 25-2). A related, but different, condition is Waldenström macroglobulinemia (WM), where late B cells produce monoclonal IgM.

MGUS

MGUS represents the earliest detectable stage for PC tumors. There appears to be some variation in the prevalence of this disease based on geography and race. Kyle and colleagues provided a long-term follow-up of 1384 patients diagnosed with MGUS from 1960 through 1994, with a median follow-up of 34.1 years (range, 0.0 to 43.6 years), residing in southeastern Minnesota. During 14,130 person-years of follow-up, MGUS progressed in 11% (147 patients), with a risk of progression, without competing causes for death, of 28% at 30 years and 36% at 40 years. Two risk factors were identified: abnormal serum free light-chain ratio (ratio of κ to λ free light chains) and a concentration of the monoclonal protein >1.5 g/dL. Patients with the non-IgM MGUS could be segregated according to these 2 risk factors as follows: those with neither had a 20-year progression risk of 7%; those with 1, 20%; and those with both, 30%.

Similarly, monoclonal protein was detected in the sera of 334 persons from among 30,279 French adults studied, translating to a prevalence of 1.1%. In a convenience sample of community-dwelling older subjects aged 63 to 95 years seen for health screening examinations, a monoclonal protein was seen in 2.7% of Japanese compared to 10% of Americans. In contrast, African Americans had a greater than 2-fold-higher prevalence of monoclonal gammopathy than Whites; the higher rate is similar to that seen among Africans living in Ghana.

The prevalence of monoclonal gammopathy increases with age and is slightly higher in men than in women. The etiology of MGUS is likely based on stochastic deleterious mutations and translocations that occur in the process of normal B-cell development. While B cells are not normally allowed to engage in DNA repair, the frequency of the mutational challenge of antigenic exposure rarely allows a mutated/translocated cell to survive and, in time, gives rise to MGUS and MM. It is quite possible, given that the greatest time of antigenic challenge to B cells is early in life, that the very first cell that later causes MGUS or MM may arise during childhood or early adulthood.

Recent studies have conclusively shown that MGUS always precedes MM and that MGUS was likely present for a long time prior to a MM diagnosis. It has been estimated that MGUS is likely to be present for 8 to 10 years (probably more) before the diagnosis of MM. While there are several alterations that have been reported in PCs and the marrow microenvironment, no single abnormality yet explains the transition to malignant disease. During this transition, which can be abrupt or protracted, either clonal PCs or the microenvironment or immunity must change. Some have proposed that decreased immune surveillance or alterations of the gene MYC may be the culprit. However, the critical events that mediate this "malignant switch" in the PCs remain unclear (Figure 25-2).

In some individuals, a monoclonal protein test is performed because an elevated total protein is detected on a blood chemistry group or an elevated sedimentation rate or rouleaux on a peripheral blood smear is found. Once the monoclonal protein is detected, it is important to determine whether any of the disease states described previously are present. The degree to which evaluation is carried out depends on the clinical situation, especially on the serum concentration of the monoclonal protein and presence of any symptoms; clinical evaluations should, at a minimum, include a complete blood count, serum calcium, serum creatinine, serum FLC assay, and a 24-hour urine collection to monitor Monoclonal (M)-protein excretion. More detailed evaluations including a bone marrow examination and imaging of the bones for lytic lesions, are not always required (particularly if the M protein is small and the patient is completely asymptomatic) but may be important

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Table 25-1 Diagnostic criteria and differential diagnosis of monoclonal gammopathies

Plasma cell disorder	Definition
Smoldering multiple myeloma	Both criteria must be met: Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10% to 60% Absence of myeloma-defining events or amyloidosis
Non-IgM monoclonal gammopathy of undetermined significance	Serum monoclonal protein <30 g/L Clonal bone marrow plasma cells <10% Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder
IgM MGUS	Serum IgM monoclonal protein <30 g/L No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly, or other end-organ damage that can be attributed to the plasma cell proliferative disorder
Light-chain MGUS	Abnormal FLC ratio (<0.26 or >1.65) Increased level of the appropriate free light chain (increased sFLC in patients with ratio >1.65 and increased sFLC in patients with ratio <0.26) No Ig heavy-chain expression on immunofixation Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder Clonal bone marrow plasma cells <10% Urinary monoclonal protein <500 mg/24 h
Solitary plasmacytoma	Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Normal bone marrow with no evidence of clonal plasma cells Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder
Solitary plasmacytoma with minimal marrow involvement	Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Clonal bone marrow plasma cells <10% Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder
POEMS syndrome	Polyneuropathy Monoclonal plasma cell proliferative disorder Any 1 of the 3 other major criteria: sclerotic bone lesions, Castleman disease, elevated levels of VEGFA Any 1 of the following 6 minor criteria: Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) Extravascular volume overload (edema, pleural effusion, or ascites) Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails) Papilledema Thrombocytosis/polycythemia

Table continues on next page

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Table 25-1 Diagnostic criteria and differential diagnosis of monoclonal gammopathies *(continued)*

Plasma cell disorder	Definition
Systemic AL amyloidosis	Presence of an amyloid-related systemic syndrome* (eg, renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement) Positive amyloid staining by Congo red in any tissue (eg, fat aspirate, bone marrow, or organ biopsy) Evidence that amyloid is light-chain-related established by direct examination of the amyloid using mass spectrometry-based proteomic analysis or immunoelectron microscopy Evidence of a monoclonal plasma cell proliferative disorder (serum monoclonal protein, abnormal free light-chain ratio, or clonal plasma cells in the bone marrow)

*Patients with serum IgM concentration <3.0 g/dL, in the absence of anemia, hepatosplenomegaly, lymphadenopathy, and systemic symptoms and minimal or no lymphoplasmacytic infiltration of the bone marrow (<10%), are considered to have an IgM MGUS rather than Waldenström macroglobulinemia.

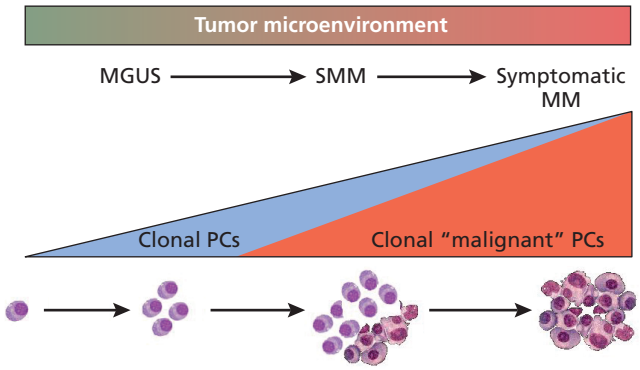
Table 25-2 Uncommon PC proliferative disorders related to or associated with a monoclonal protein

Diagnosis	Presenting features
Scleromyxedema	Generalized papular and sclerodermoid cutaneous eruption with waxy firm papules and plaques with mucin deposition, increased fibroblast proliferation, and fibrosis on histologic examination Systemic manifestations may involve the cardiovascular, gastrointestinal, pulmonary, musculoskeletal, renal, or nervous systems Monoclonal gammopathy is usually IgG with a predominance of λ light chains
Capillary leak syndrome	Rare disorder characterized by episodes of severe hypotension, hypoalbuminemia, and hemoconcentration associated with extravasation of intravascular fluid. Patients have elevated levels of vascular endothelial growth factor and angiopoietin 2. Typically, a prodromal phase is followed by an extravasation phase with edema, hypotension, and hemoconcentration, sometimes with compartment syndrome.
Schnitzler syndrome	Chronic urticaria associated with IgM monoclonal gammopathy typically IgM κ May also have bone pain, skeletal hyperostosis, arthralgias, lymphadenopathy, and intermittent fevers
TEMPI syndrome	Rare constellation of telangiectasias, erythrocytosis with elevated erythropoietin, MGUS, perinephric fluid collections, and intrapulmonary shunting Favorable responses have been with the proteasome inhibitor bortezomib

in young patients (especially those younger than 50 years) with risk factors for disease progression (Table 25-3).

Once a more aggressive PC disorder is diagnosed, a more comprehensive workup is important. For instance, one must check for the presence of MM or immunoglobulin light-chain amyloidosis (or other related conditions). Patients with MGUS have a fixed ~1% per year risk of progression, translating to roughly a 20% progression rate at 25 years from diagnosis. Various prognostic factors predicting for increased risk of disease progression, typically to MM, have been described (Table 25-3). When a new monoclonal protein is detected, by necessity, the cross-sectional nature of that detection precludes determination of imminent progression. Accordingly repeat testing in 3-6 months should be done.

Figure 25-2 The transition from MGUS to myeloma.



The management of MGUS is based on the expectant observation of patients, monitoring for progression. Patients should have periodic evaluations that include a complete blood count, serum calcium, serum creatinine, and a 24-hour urine collection for protein electrophoresis. Risk-based monitoring is likely appropriate, with those at lower risk (ie, those with an IgG monoclonal

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Table 25-3 Factors associated with increased risk of progression in MGUS

1. Higher M-protein levels at diagnosis★
2. Non-IgG monoclonal protein★
3. Extreme abnormalities of the FLC ratio★
4. Percentage of PCs in bone marrow
5. Suppression of uninvolved Igs
6. Presence of circulating PCs or clonal B cells
7. Bone density abnormalities
8. Advanced age
9. Bence Jones proteinuria
10. Increasing M-protein concentration
11. Imaging evidence of neoplastic deposits by MRI or PET
12. High-risk genetic markers
13. High number of abnormal plasma cells

M, monoclonal.

★A combination of M protein ≥1.5 g/dL or 15 g/L, non-IgG M protein and an abnormal serum free light-chain ratio (κ:λ ratio) has been shown to identify persons at the highest risk of progression.

protein, <1 g/dL) having evaluations every 2-3 years with the rest of the patients being followed annually. Younger individuals are usually monitored more closely. The 2 most dreaded features of MM CRAB (C, calcium elevation; R, renal impairment; A, anemia; B, bone involvement) symptoms are bone disease and renal failure. Renal failure, namely cast nephropathy, can be predicted by the serum concentration of the free light chain; those with sFLC elevations of less than 100 mg/dL are at low risk for renal damage.

Light-chain MGUS

A small proportion of patients with monoclonal PC proliferation may not secrete an intact Ig monoclonal protein, but rather a κ or λ light chain only. Light-chain MGUS has been defined as an abnormal free light-chain ratio with no heavy-chain expression, plus increased serum concentration of the involved light chain. In a large study, prevalence of light-chain MGUS was 0.8% (95% confidence interval [CI], 0.7%-0.9%), contributing to an overall MGUS prevalence of 4.2% (3.9%-4.5%). The median age of patients with light-chain MGUS was 68 years (range, 50.0-96.0 years) compared with 70 years (range, 50.0-96.0 years) for those with conventional MGUS. Risk of progression to MM in patients with light-chain MGUS was 0.3% (range, 0.1%-0.8%) per 100 person-years, in contrast to 1 per 100 person-years for conventionally defined MGUS. All progressions of light-chain MGUS were to light-chain MM. Renal disease was relatively more frequent in this population, with 23% of 129 patients with light-chain MGUS being diagnosed with renal disease.

Biclonal gammopathies

A simultaneous presence of 2 distinct monoclonal proteins can be seen in as many as 5% of patients with monoclonal gammopathies. This situation likely represents the proliferation of 2 separate clones of PCs producing M proteins of different Ig classes, often with a different light chain. In one study, 20 (2%) of 1034 patients with monoclonal gammopathy had 2 distinct monoclonal spikes; 3 were associated with lymphoma, 7 with myeloma, 9 with MGUS, and 1 with an autoimmune rheumatologic condition.

Smoldering (or asymptomatic) MM

Development of MM is invariably preceded by a distinct MGUS phase as has been demonstrated by recent studies. However, an intermediate phase can be identified in a number of patients demonstrating an increasing tumor burden characterized by increased M protein levels (serum M protein ≥3 g/dL or urinary monoclonal protein ≥500 mg per 24 h) or increasing marrow plasmacytosis (clonal bone marrow plasma cells, 10% to 60%). This intermediate phase in the disease evolution is characterized by increasing tumor burden, but not quite at the level that would cause end-organ damage. Sometimes the first instance of diagnosis of a plasma cell tumor is at the smoldering multiple myeloma (SMM) stage. There is much debate as to whether SMM should be even further divided into those cases that resemble MGUS more and those that seem more like active MM.

The ongoing risk of progression to MM from SMM is much greater than that for MGUS. The risk of progression is 10% per year for the first 5 years (cumulative 50% at 5 years), 5% per year over the subsequent 5 years (cumulative 15% for years 6-10; cumulative 65% for the first 10 years) and 1% per year thereafter. The risk of progression from SMM to active MM is similarly dictated by the same factors that describe higher risk of progression from MGUS to MM (Table 25-4). A prognostic score was recently developed by the Mayo Clinic proposes 3 subgroups of SMM with different risks of progression to active MM. The 3 criteria include a plasmacytosis greater than 20%, an M-spike of greater than 2 g/dL, or a serum free light-chain ratio (abnormal/normal) greater than 20. The 3 groups are defined by none of these factors, 1, or 2 or more, with relative risk of progression for the intermediate and high-risk groups of 2.25 and 5.63 respectively. The International Myeloma Working Group (IMWG) further expanded the risk stratification by adding high-risk cytogenetic abnormalities as a risk factor. The probability of

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Table 25-4 Factors associated with increased risk of progression of SMM to MM

1. Higher M-protein levels at diagnosis
2. Abnormal FLC ratio
3. Percentage of PCs in bone marrow
4. Suppression of uninvolved Igs
5. Presence of circulating PCs
6. A high predominance of abnormal PCs (≥95%) (defined by phenotype and flow-based assessment) from the total PCs in the marrow
7. Presence of FISH abnormalities (t(4;14), deletion 17p, gain 1q21, and hyperdiploidy)
8. IgA isotype
9. Evolving M component

M, monoclonal.

progression at 2 years for the low, low-intermediate, intermediate, and high-risk groups are to be 6%, 23%, 45% and 63% respectively.

The Spanish group classifies patients for risk of progression based on the percent of PC that have an aberrant phenotype (high risk if ≥95% of the total PCs are clonal) and immunoparesis (suppression of the uninvolved Igs). The median time to progression is 23 months when 2 risk factors are present, 73 months when only 1 risk factor is present, and not reached when none of the risk factors are present. Other factors that predict risk of progression to MM include elevation of the serum concentration of the free light chain (FLC), increases in levels of the monoclonal proteins, and high-risk genetic abnormalities detected by fluorescent in situ hybridization (FISH), including t(4;14), gain of 1q21, or hypodiploidy. Both the Mayo and the Spanish criteria can identify patients that have a 70% risk of progression at 3 years. Recognizing that some SMM are at very high risk of progression, new criteria to initiate therapy have been proposed by the International Myeloma Working Group and include the presence of FLC ratio ≥100, a plasmacytosis greater than 60%, and 2 or more focal bone or marrow lesions each of at least 5-mm size on magnetic resonance imaging (MRI). The median time to progression to symptomatic MM for SMM patients having these features is 2 years. These patients are now considered to have early myeloma, and they should be candidates for immediate treatment.

In 2022, the standard of care for patients with SMM remains expectant observation, although 2 randomized clinical trials have explored the role of lenalidomide treatment as a prevention treatment, both with positive results. Patients need to be carefully staged, and risk of progression should be determined using one of the aforementioned systems. Of the 4 CRAB criteria, 2 have the potential to cause long-lasting consequences: bone damage and renal failure. The serum concentration of the free light chains is a good predictor of the risk of renal damage, with concentrations above 1000 mg/L increasing this risk. Patients with low concentrations of the serum free light chain are at low risk for renal damage and thus their surveillance can be more sporadic. There are no good biomarkers that can predict future damage to bone structure. Initially, a complete imaging process that includes, at a minimum, a positron emission tomography (PET) scan, low-dose whole-body computed tomography (CT) scan, low-dose whole-body CT scans or MRI is recommended. The use of traditional imagining such as was done by the bone survey, which lacks sensitivity, is no longer recommended.

Several clinical trials are exploring the possibility of earlier intervention for patients with SMM. The purpose behind this clinical research is to develop strategies to prevent complications associated with progression to active MM and to improve survival of patients. The first of these trials has been reported and updated where early treatment with lenalidomide and dexamethasone appeared to be beneficial for SMM patients as compared to observation only, including improved overall survival (OS). Another published trial (E3A06) compared lenalidomide (as a single agent) to placebo, and was favorable for progression-free survival (PFS) in favor of the therapeutic intervention. Other clinical trials are now exploring active combinations being used in the treatment of active MM, as well as novel agents, such as daratumumab. The readout for these trials with regard to time-dependent variables will require sufficient periods of follow-up, but the early readings regarding response rates are very promising.

Idiopathic Bence Jones proteinuria and light-chain SMM

Patients may occasionally present with isolated monoclonal free light chains in the urine, or Idiopathic Bence Jones proteinuria (IBJP). Bence Jones is synonymous with light chains. Unlike the intact Ig molecule, the molecular size of free light chains allows them to be filtered down into the urine. While the criterion to establish IBJP is an excretion of 200 mg of light chains or more in a 24-hour period, there are other criteria that can apply. Usually, patients are also required to have no monoclonal protein in the serum, no overt evidence of MM, and no AL amyloidosis clinical features or other related plasma cell proliferative disorders. A related entity has been identified that is associated with clonal expansion analogous to SMM but which produces only free light chains.

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Active (symptomatic) MM

The term MM is reserved for those clinical situations where the clonal expansion of PCs leads to evidence of end-organ damage, now referred to as a myeloma-defining event, and there is an indication for treatment. It is important to note that the World Health Organization defines a diagnosis of plasma cell myeloma when the pathology analysis reveals more than 10% PCs, even when the person does not fulfill evidence of end-organ damage. The clonal expansion of PCs can lead to bone destruction (in the majority of patients with active MM), renal insufficiency, anemia, and, in cases of extreme bone resorption, hypercalcemia. Other complications are possible, such as protein-associated complications or infections associated with immunosuppression.

Epidemiology

MM accounts for 1% of all malignancies and 10% of all hematological malignancies. In 2021 the American Cancer Society reports that the lifetime risk of getting multiple myeloma is 1 in 132 (0.76%). About 34,920 new cases will be diagnosed (19,320 in men and 15,600 in women), and about 12,410 deaths are expected to occur (6840 in men and 5570 in women). SEER (surveillance, epidemiology, and end results) data from 1992 through 1998 show an overall incidence of 4.5 cases per 100,000 per year, with the incidence among whites of 4.2 per 100,000 per year and among African Americans of 9.3 per 100,000 per year. In contrast to the higher incidence in persons of African descent, the incidence of MM is lower in Asian and Hispanic populations, and there is a slight male preponderance. The median age at diagnosis is 65 to 70 years.

Etiology

While the precise cause of MM, if any, has not been identified, the knowledge we have regarding the ontology and anatomy of genetic markers leads to the logical conclusion that, in most cases, MM is a consequence of an accident in nature during the normal process of B-cell development. The majority of specific genetic markers can be logically traced to steps of B-cell maturation, such as class switching or somatic hypermutation. While environmental factors may increase the risk of these stochastic genetic aberrations it is unlikely that a specific insult is responsible in the majority of cases. For instance, exposure to ionizing radiation may increase the risk, such as was seen in the atomic bomb survivors in Hiroshima, Japan, but it is likely that, in most cases, ionizing radiation exposure is not causative. Chemical agents have been epidemiologically linked but there is a large array of possibilities and likely none are predominant. It is likely that, in some cases, families have a genetic susceptibility to develop the disease. Epidemiological studies have shown an increase in the risk of plasma cell neoplasms in family members, but the disease is rare enough that the absolute increase is largely insignificant. There are some families who are affected with clustering of the disease with several members afflicted. Up to now no specific associations have been identified with familial cancer genes.

Some of the strongest data in support of genetic susceptibility come from the observation of an increased incidence (2:1) of MM in African Americans in comparison with Whites. This incidence was further corroborated by the observation that the prevalence of MGUS was twice as high in serum samples from a blood bank from Ghana as in White patients. Genetic-susceptibility genes have not been conclusively identified, although, in some cases, loci have been identified. The genetic aberrations of clonal plasma cells in African Americans can be different from those of White persons, but, for the most part, the cells are quite similar. A series of recent studies have linked autoreactivity to paratarg-7 as a risk factor in as many as 30% of cases, but the results remain under investigation. Large epidemiologic studies are being conducted in Iceland to better understand prevalence and genetic linkage of MGUS.

Pathogenesis

Studies derived from the serial storage of serum samples of Army recruits conclusively showed that MM is always preceded by MGUS. The duration of this anticipatory diagnosis is usually several years (8 to 10) prior to onset of symptoms. The specific changes that lead to the transformation of MGUS to MM remain unidentified but are suspected to arise from a combination of acquisition of new genetic changes (on a stochastic fashion) with probable loss of immune surveillance. While most of the comparative genetic studies have not found predictability in the acquisition of genetic progression events, a few changes are notable. Some of the genetic events considered to be associated with progression are less prevalent in MGUS, such as -17p13, 1q amplification, and certain mutations (*RAS*). Abnormalities associated with *MYC* signaling have also been described as more common with active MM and include IgH-associated translocations, non-IgH rearrangements, and a gene-expression profile signature characteristic of *MYC* expression. While multiple subclonal models for progression have been proposed, there is no empirical validation of their importance other than the

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fact that the more genetic instability, usually a surrogate of high-risk genetic features, the more likely there will be diversified expansion of subclones leading to more aggressive disease.

Genomic abnormalities

Nearly all MM cells harbor genetic and chromosome abnormalities in the monoclonal plasma cells. Primary abnormalities (eg, translocations) are usually present in all PCs and persist through the course of the disease; a t(11;14) variant MM will always be a t(11;14) MM. At the top level, 2 major types of MM exist, hyperdiploid MM associated with the presence of multiple trisomies, and nonhyperdiploid MM associated with chromosome 14q32 translocations and enriched for high-risk disease. Although, in some cases, both hyperdiploidy and IgH translocations are reported, for the most part, these 2 categories are mutually exclusive.

IgH translocations

About 45% of MM cases harbor IgH translocations at the locus 14q32. These translocations mostly involve rearrangements that occur at the time of isotype class switching of the Ig heavy-chain region. Whether these rearrangements occur only as random stochastic events ("bad luck") versus their being associated with constitutive failure to properly repair these breaks or other precipitating factors remains unknown. These translocations are unique in that, in many cases, the nature of the separation of the IgH enhancers can lead to overexpression of putative oncogenes of the 2 derivative chromosomes. The most common translocations involve chromosome 11q13 (*CCND1*) in 15% of cases, 4p16 (*FGFR/MMSET*) in another 15% of cases, 16q23 (*MAF*) in 5% of cases, and 6p21 (*CCND3*) and 20q11 (*MAFB*) in lower proportions of patients. It should be noted that these translocations can be present since the early stages of the plasma cell tumors, such as MGUS, without progressing to MM over many years. The translocations seem to be necessary (in some cases) but not sufficient to cause MM.

Notable clinical correlation associated with these translocations have been identified. For patients with t(11;14), the advent of venetoclax as a targeted agent promises to have an impact in the natural history of the disease. Patients with t(4;14) have a much-improved prognosis because of the administration of proteasome inhibitors (PIs).

Gains and losses of chromosomal material

As previously mentioned, patients with MM can be grouped into 2 major categories according to their ploidy status: hyperdiploid and nonhyperdiploid. The ploidy status can be assessed by karyotyping (not clinically recommended anymore due to its low sensitivity), flow-based approaches, or inferred indirectly by the presence of trisomies in FISH analysis. The usual chromosome count of hyperdiploid patients is close to 53, which happens mostly as a consequence of trisomies of the odd-numbered chromosomes with the exception of chromosome 13. Nonhyperdiploid MM is characterized by a very high prevalence of *IGH* translocations involving the 5 recurrent partners described previously. Likewise, monosomy/deletion 13 and gains on 1q occur more commonly in nonhyperdiploid MM.

Loss of chromosome 13 is the most common (~50% of cases) genetic loss in MM (85% monosomy, 15% interstitial deletions) and is strongly associated with *IGH* translocations, but chromosome loss can also be observed in cases of hyperdiploidy. Other progression genetic events include deletions of 17p13 (10% at new diagnosis), and gains on 1q (40%-50% of newly diagnosed patients). The loss of the short arm of chromosome 17, which leads to the loss of heterozygosity of *TP53* and associated mutations, is rare. The incidence of 17p13 deletions and mutations of TP5 increases with advancing stages of the disease and is observed in 20% of patients at the time of first relapse and up to 80% of patients with plasma cell leukemia.

Recent studies have demonstrated lesions of chromosome 1 as one of the most common abnormalities in MM (~40% of cases); mostly these lesions are 1q gains as the result of tandem duplications and jumping segmental duplications of the chromosome 1q band. Recently, studies have also shown that 1p losses (especially 1p22 and 1p32 deletions) are also frequent in MM patients, are highly linked with 1q amplifications, and are also associated with a more adverse outcome. It is important to highlight that the highly aggressive variants of MM more likely occur only when PCs have 4 or more copies of 1q (ie, amplification) and not a mere gain (ie, 3 copies). A recent proposal has been made to classify patients who have biallelic inactivation of TP53 and 1q amplification, in the context of R-ISS Stage III, as the "double hit MM."

Mutations detected by whole-genome sequencing

Whole-genome sequencing strategies have shown that there are approximately 35 nonsynonymous mutations per myeloma sample. One study including 203 patients has shown that 131 (65%) had evidence of mutations in 1 or more of 11 recurrently mutated genes: *ACTG1, RB1, CYLD, PRDM1, TRAF3, BRAF, FAM46C, DIS3, TP53, NRAS,* and *KRAS.* Interestingly, mutations were often present in subclonal populations, and multiple mutations within

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the same pathway (eg, RAS and BRAF) were observed in the same patient. The complex MM mutational signature is similar to other hematological malignancies, such as acute myeloid leukemia, but is in contrast to hairy cell leukemia and WM, in which single unifying mutations are seen (*BRAF* and *MYD88*, respectively). Several groups are working with targeted panels to determine prospectively the prevalence of the clinical significance of these mutations.

Subclonal evolution

Several studies have now shown the subclonal nature of MM PCs. Single cell analysis using FISH probes has shown that there are various subpopulations of PCs, even though all of these cells are similar in their core genetic changes. The practical introduction of this information into the clinic, while not specific, has led to the conceptual framework where a comprehensive approach that eradicates all MM, particularly those that are more aggressive, is important as treatment is initiated. Strategies that aim to control, or simply to palliate, the disease run the risk of enriching cells for aggressiveness, and yet, in some cases, attenuated treatment can lead to long duration of disease control.

Multiple myeloma and bone disease

Lytic bone lesions are one of the hallmarks of MM and are observed in at least 85% of cases. Bone disease can present with diffuse osteopenia, discrete lytic lesions, or large destructive lesions leading to pathological fractures. These destructive lesions are the culmination of an altered balance between the osteoblastic and osteoclastic activity leading to net bone resorption. A number of signaling factors have been implicated and include RANK (receptor activator of NF-κB) ligand, RANK-ligand, macrophage inflammatory protein (MIP)-1a, activin A, vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), IL-3, IL-7, TNF-α, IL-6, IL-1β, DKK1, and MIP-3α. RANK-L binds to its functional receptor RANK (TNF-receptor superfamily) on osteoclasts, stimulating osteoclastogenesis and inducing bone resorption. Osteoprotegerin (OPG) works as a soluble decoy receptor inhibiting the activity of RANK-L and results in bone anabolism. In MM, this balance is disrupted by increased expression of RANK-L and decreased expression of OPG on stromal cells as a result of their interaction with MM cells. MIP-1a potently stimulates osteoclast formation through enhancing the activity of RANK-L and directly stimulating osteoclast differentiation.

A number of agents have been used to prevent bone destruction in MM. A clinically beneficial effect was first noted for bisphosphonates, including pamidronate or zoledronic acid. Initially these agents were used in an indefinite fashion, but long-term administration was associated with a process called osteonecrosis of the jaw (ONJ). This process occurs as a consequence of avascular osteomyelitis resulting from vascular ischemia caused by the impingement of blood vessels located in the cancellous bones of the mandible. The anatomy of the mandible, 2 strong cortical plates with only a small cancellous bone center cause this bone structure to be at risk. Accordingly, ONJ occurs only in the mandible and not usually anywhere else, including the upper maxillary. More recently denosumab has been approved for the prevention of bone lesions in MM. Denosumab is administered subcutaneously on a monthly basis. A phase 3 trial showed noninferiority for denosumab, and it even showed an improvement in progression-free survival. Denosumab is not associated with renal toxicity like bisphosphonates are, and thus should be preferred in patients with impaired renal function. The pathophysiology of ONJ was further confirmed by the fact that another anabolic drug, denosumab, also caused this serious complication.

Clinical presentation and diagnostic considerations

The presentation symptoms and clinical picture of MM can lead to one of the common complications including fatigue, bone pain, easy bruising and bleeding, recurrent infections. The criteria that define progression of myeloma are best remembered by the acronym "CRAB" (calcium elevation, renal dysfunction, anemia, and bone disease) features. The common symptoms and the underlying pathology are detailed in Table 25-5.

The initial workup should be aimed at confirming the diagnosis, estimating the tumor burden, assessing the severity of disease-related complications, and gathering the data for risk stratification. The typical testing associated with the initial workup is detailed in Table 25-6.

Newer imaging techniques have greater sensitivity than radiographic bone survey for detection of MM bone lesions. CT has the highest sensitivity for the detection of bone lesions, and, with the whole-body low-dose modality, the radiation exposure is much lower than with conventional CT. Magnetic resonance imaging has the highest resolution for soft tissue and bone marrow infiltration, but it is inferior to CT for assessment of bone disease. Finally, positron emission tomography allows assessment of tumor metabolism and disease activity. CT, MRI, and PET should be preferred over simple bone survey imaging due to the low sensitivity of the latter.

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Table 25-5 Clinical presentation of MM

Symptoms and signs	Mechanism
Anemia	Marrow infiltration, direct destruction of erythroblasts, anemia of renal failure
Easy bruising and bleeding	Thrombocytopenia, acquired von Willebrand disease or inhibition of other clotting factors by monoclonal protein
Bone pain	Lytic bone lesion, pathologic fractures
Fatigue	Anemia, hyperviscosity, renal failure
Recurrent infections	Hypogammaglobulinemia, suppressed cellular immunity, neutropenia
Altered mental status, confusion	Hypercalcemia, hyperviscosity
Neurological deficits	Cord compression due to paraspinal mass/vertebral fractures, nerve compression from plasmacytomas

Staging and risk stratification: prognostic factors

As with all malignancies, staging systems have been developed for MM. A historic system was the Durie-Salmon staging system, but this system should no longer be used. It was replaced by the International Staging System (ISS) which incorporates 2 readily available laboratory parameters; serum concentration of the albumin and β_2-microglobulin (see the following). The staging system, a purely a prognostic classification, has served well to compare clinical trials, but it does not necessarily guide therapy. The most recent version now incorporates genetic markers of high-risk disease and the serum lactate dehydrogenase (LDH) to further identify dissimilar outcomes for patients. More recently a revised international staging system (R-ISS) has been now presented where the original ISS is further refined by the addition of high-risk genetic features and an elevated LDH. The 3 R-ISS categories have a 5-year overall survival of 82%, 62%, and 40%. Well-accepted prognostic factors and risk-stratification systems are detailed in Tables 25-7 and 25-8.

MM is a heterogeneous disease in terms of outcomes, with nearly a quarter of patients dying within the first 2-3 years following diagnosis and a similar fraction living >10 years. In recent times, there has been increased effort toward identification of the patients with high-risk myeloma. The main drivers of the heterogeneity in outcome are the genetic abnormalities seen in myeloma. The canonical classification of high risk identifies patients harboring del17p, t(4;14), and t(14;16). It is not clear yet what the clinical implications are for other MAF translocations, such as t(14;20). This system can be improved by utilizing gene-expression profiling or mutational analysis of other relevant genes.

Response to frontline therapy is one of the most important prognostic factors in most hematological

Table 25-6 MM: important tests in evaluation

Complete blood count, including differential to assess for circulatory PCs
Chemistry with BUN, creatinine, calcium, LDH
Serum protein electrophoresis with immunofixation
Quantitative Igs
24-h urine protein electrophoresis with immunofixation
Serum-free light chain
Skeletal survey (plain films or whole-body low-dose CT)
Serum β_2-microglobulin, albumin
Bone marrow aspirate and biopsy
FISH, gene expression and genetic mutation panels
MRI,* PET scan*

BUN, blood urea nitrogen; CRP, C-reactive protein.

*MRI and PET scans are used in specific circumstances and are not routinely performed in all patients.

Table 25-7 Prognostic factors in MM

Tumor-related prognostic factors	Host-related prognostic factors
FISH: del17p, t(4;14), t(14;16), amplification of 1q (4 copies or more) or biallelic inncativation of TP53	Advanced age
High lactate dehydrogenase level	Poor performance status
High-risk gene-expression profile signature	Faril status
Unable to attain MRD-negative status after treatment initiation	Comorbidities
High β_2-microglobulin level (International Staging System stage III)	Renal failure
Presence of circulating PCs	
High PC proliferative rate (eg, measured by the S phase)	
Presence of extramedullary disease	

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Table 25-8 Revised International Staging System

Stage	Criteria	5-y overall survival (%)
R-ISS I	ISS-I (serum β_2-microglobulin <3.5 mg/L, serum albumin ≥3.5 g/dL) plus standard-risk genetics and no LDH elevation	82
R-ISS II	All others	62
R-ISS III	ISS III (serum β_2-microglobulin ≥5.5 mg/L) plus elevated LDH or high-risk genetics	40

malignancies—MM being no exception—whereby the better the quality of the response, the longer the survival. Patients achieving complete response (CR) display significantly longer survival compared to partial responders (PRs); moreover, patients failing to achieve at least PR with an optimized induction therapy should be considered high-risk patients with a survival of <2 years. However, the definition of CR is far from optimal, and more sensitive techniques for evaluating minimal residual disease (MRD) have shown in recent studies to be better predictors of long-term outcomes for MM patients. The evaluation for and monitoring of minimal residual disease will be reviewed further in the following.

Treatment approaches for MM

The treatment paradigms for MM have changed dramatically during the past decade as result of improved understanding of the biology of the disease, better risk assessment, availability of more effective antimyeloma agents, systematic use of autologous stem cell transplantation (ASCT), and better appreciation of the importance of supportive care. The median overall survival in MM has improved to 8 to 10 years or more for patients treated optimally by expert clinicians and to 2- to 3-fold overall, according to data from large national databases, such as SEER and claims based on real-world datasets. The overall approach and goals are summarized in Figure 25-3. A sequential approach to newly diagnosed MM includes risk stratification/prognostication, immediate interventions for reversal of acute disease-related complications, initiation of systemic therapy with the goal of maximizing the response benefit, consolidation and maintenance strategies designed to improve the depth and duration of the response achieved initially, and consistent use of supportive care strategies along the entire course. Unfortunately, in the current era, the majority of patients relapse after initial disease control, and additional therapies need to be employed for continued control of MM.

Whether MM is curable is an issue of semantic definition. Some patients have long-lasting disease control with therapy and yet have residual and threatening disease. Other individuals who receive successful initial therapy, usually including autologous stem cell transplantation, achieve long-lasting remissions and never again require therapy. This small fraction of patients (probably less than 10%-20% of all cases) can effectively be considered cured. However, the majority of patients ultimately relapse and need subsequent lines of therapy.

IMWG has developed a set of uniform response criteria for disease assessment in MM (Table 25-9). These criteria are based on the measurement of serum biomarkers but now also incorporate other markers that probe further to determine the depth of true response (MRD and PET).

Figure 25-3 Stages in the initial management of MM.

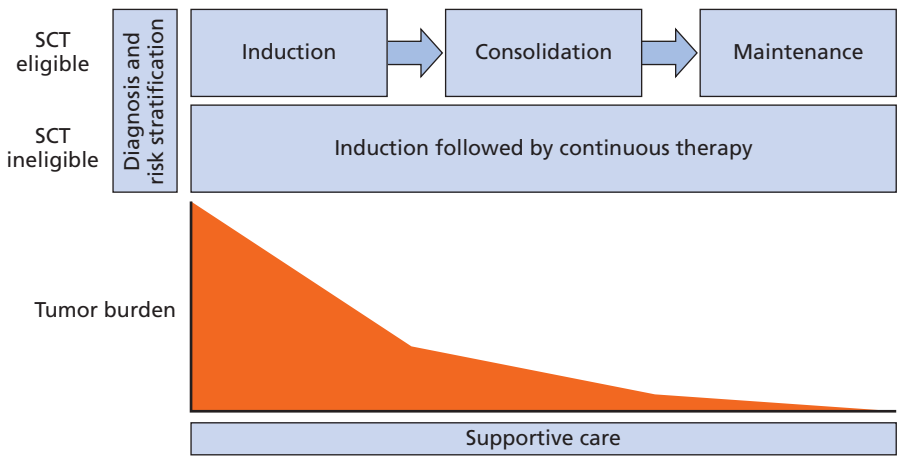

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Table 25-9 Response and relapse definitions (IMWG 2016)

	Response criteria
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD negative	MRD negativity in the marrow (next-generation flow cytometry [NGF], next-generation sequencing [NGS], or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD negative at 5 years).
Flow MRD negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Sequencing MRD negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the Clonoseq platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Imaging plus MRD negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less than the mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue.
Standard IMWG response criteria	
Stringent complete response	Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells).
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates.
Very good partial response	Serum and urine M protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M protein plus urine M-protein level <100 mg/24 h.
Partial response	≥50% reduction of serum M protein plus reduction in 24-hour urinary M protein by ≥90% or to <200 mg/24 h. If the serum and urine M proteins are not measurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M proteins are not measurable, and serum free light-chain assay is also not measurable, ≥50% reduction in plasma cells is required in place of M protein, provided baseline bone marrow plasma cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required.
Minimal response	≥25% but ≤49% reduction of serum M protein and reduction in 24-h urine M protein by 50% to 89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease.
Progressive disease	Any 1 or more of the following criteria: Increase of 25% from lowest confirmed response value in 1 or more of the following criteria: • Serum M protein (absolute increase must be ≥0.5 g/dL) • Serum M protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL • Urine M protein (absolute increase must be ≥200 mg/24 h) • In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma cell percentage irrespective of baseline status (absolute increase must be ≥10%) • Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis • ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

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Table 25-9 Response and relapse definitions (IMWG 2016) *(continued)*

	Response criteria
Clinical relapse	Clinical relapse requires 1 or more of the following criteria: • Direct indicators of increasing disease and/or end-organ dysfunction (CRAB features) related to the underlying clonal plasma cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression) • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD of the measurable lesion • Hypercalcemia (>11 mg/dL) • Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions • Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma • Hyperviscosity related to serum paraprotein
Relapse from complete response (to be used only if the end point is disease-free survival)	Any 1 or more of the following criteria: • Reappearance of serum or urine M protein by immunofixation or electrophoresis • Development of ≥5% plasma cells in the bone marrow • Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia [refer to Clinical relapse above])
Relapse from MRD negative (to be used only if the endpoint is disease-free survival)	Any 1 or more of the following criteria: • Loss of MRD-negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma) • Reappearance of serum or urine M protein by immunofixation or electrophoresis • Development of ≥5% clonal plasma cells in the bone marrow • Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

Initial therapy for newly diagnosed MM

It is important to ensure that the patient truly requires therapy; currently, patients with early phases of the plasma cell tumors and without complications should generally not be treated outside of a clinical trial (see aforementioned description of SMM). The goals of the initial therapy are to control the disease process rapidly and to reverse complications of the disease, such as renal failure and hypercalcemia. These goals should be accomplished while minimizing toxicity because the longer survival of patients can be marked by diminished quality of life associated with treatment toxicities. Most current regimens do not incorporate stem cell–damaging agents like melphalan, so stem cell collection is rarely impeded. However, the classical scheme where an early decision as to whether a patient should be considered a SCT candidate still applies, and this determination is done early on. Effective and safe MM therapy can greatly reduce the morbidity and mortality of patients in these critical months after diagnosis. This has resulted in improvements in overall survival for patients. These interventions include practical variations, such as lower-dose use of dexamethasone, use of prophylactic antibiotics and antivirals, and subcutaneous administration of bortezomib.

For the majority of younger patients (younger than age 65, although many patients up to the age of 75 are also offered the therapy) and for fit and healthy older individuals, SCT should be considered. Definition of SCT eligibility varies across regions and practices and is typically based on age, no limiting comorbidities and a good overall performance status. However, many of the currently used initial treatment regimens incorporating the newer drugs do not significantly impact the ability to collect stem cells and, as a result, the need to classify patients based on transplantation eligibility has diminished over time. Many combination regimens have been studied during the initial treatment phase of MM, incorporating old and new drugs; the most commonly used regimens are discussed in the following in detail, and the individual drugs and classes are listed in Table 25-10.

Treatment of transplantation-eligible patients

Before initiation of stem cell collection, patients with newly diagnosed MM receive induction therapy for 4 to

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Table 25-10 Commonly used classes of drugs in myeloma and new investigational drugs

Class	Common drugs
Older agents	
Alkylating agents	Melphalan, cyclophosphamide, bendamustine
Anthracycline	Liposomal doxorubicin
Corticosteroids	Dexamethasone, prednisone, methylprednisolone
Immunomodulators	Thalidomide, lenalidomide, pomalidomide
Proteasome inhibitors	Bortezomib, carfilzomib, ixazomib
Histone deacetylase inhibitors	Panobinostat
Monoclonal antibodies	Daratumumab (anti-CD38), elotuzumab (anti-SLAMF7). Isatuximab (anti-CD38)
Antibody drug conjugates	Belantamab mafodotin (anti-BCMA)
Chimeric antigen receptor T cells	Idecabtagene vicleucel (anti-BCMA)
Other	Meflufen flufenamide, selinexor
In development	
Bcl2 inhibitor	Venetoclax
T-cell engagers	CAR T cells, bispecific antibodies
Immunomodulator	Iberdomide

6 cycles, with the intent of disease control and reduction of tumor burden. Some of the MM-associated symptoms and comorbidities can be quickly resolved (anemia, hypercalcemia, and constitutional symptoms), and some are prevented only from progressing (bone destruction). Renal failure is its own unique category because it can sometimes be reversed in the face of active chemotherapy and rapid disease control. A previously undiagnosed renal-failure state should be considered an oncologic emergency in the case of MM, and therapy should be promptly initiated. The use of plasma exchange for light chain cast nephropathy is reviewed in the "Supportive care" section. Also, expeditious management of hypercalcemia, which can contribute to neurocognitive defects and renal failure, is also indicated. This is mostly done via administration of intravenous fluids to force diuresis, and corticosteroids, bisphosphonates, or denosumab. Ultimately, the best treatment for hypercalcemia is treating MM itself.

While many clinical trials tested various chemotherapeutic options and novel agents in combination, these studies are no longer relevant and are only of historic interest since we no longer use these agents. The modern management of MM dictates that SCT eligible patients should be treated with triplet combinations, most commonly the combination of bortezomib, lenalidomide, and dexamethasone (VRd) or, in some cases, carfilzomib, lenalidomide, and dexamethasone (KRd). These regimens are associated with a very high rate of disease response, and, in some cases, even CR without SCT. One SWOG S0777 showed clear superiority of VRd over Rd alone. The E1A11 trial comparing VRd versus KRd in the frontline setting for standard-risk patients, has been published and was negative – it failed to show the superiority of carfilzomib over bortezomib in standard-risk disease. The study was not one of equivalency and highlights the trade-offs between both regimens. Patients treated with bortezomib more commonly have peripheral neuropathy (most of which is permanent) while patients treated with carfilzomib have a higher incidence of cardiorenal toxicity (while more serious, it is reversible in many cases). Either regimen is appropriate as frontline therapy and both combinations are being tested in ongoing clinical trials. Until recently we used the combination of cyclophosphamide, bortezomib, and dexamethasone (CyBORD) as induction therapy, but the results of a randomized comparison between CyBORD and a regimen similar to VRd, that uses thalidomide instead of lenalidomide (VTD), showed that this regimen was superior to CyBORD. CyBORD is now only recommended for patients with AL amyloidosis (in combination with daratumumab or MM with acute renal failure, given that it can usually be administered immediately. In countries where frontline lenalidomide is not available, other bortezomib-based triplets, including bortezomib-thalidomide-dexamethasone (VTD) in combination with daratumumab (CASSIOPEA).

Four-drug combinations are being investigated, and appear to result in deeper responses, including a high rate of MRD negativity. One randomized phase 2 trial explored the combination of daratumumab plus VRd (GRIFFIN). Two single arm trials have tested the combination of daratumumab with KRd, with SCT (MASTER trial) and without it (Manhattan trial).

Role of high-dose therapy and autologous stem cell transplantation

The role and timing of SCT is now being challenged by the efficacy of continuous treatment with novel agents and have led many investigators to suggest reserving SCT for the time of relapse. While the MM community spent its first 20 years of coordinated clinical research proving that SCT was an effective treatment modality, the current and future years will test whether SCT is still a necessary requirement for optimal outcomes. Older studies prior to

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the advent of novel therapeutics had suggested that delaying SCT was associated with similar survival outcomes.

A report of pooled data from 791 patients enrolled in similar prospective phase 3 randomized Italian trials for newly diagnosed MM patients younger than 65 years, both using lenalidomide-dexamethasone induction followed by SCT (early transplantation) versus 6 cycles of conventional chemotherapy (melphalan or cyclophosphamide) plus lenalidomide and steroids and, followed by lenalidomide-based regimens or placebo as maintenance. In both trials, patients assigned to nontransplantation arm received SCT at relapse (delayed transplantation). Early SCT improved PFS1 (3-year rate: 59% versus 35%, $P < 0.001$) and PFS2 (3-year rate: 77% versus 68%, $P = 0.01$), and marginally improved OS (4-year rate: 83% versus 72%, $P = 0.09$) in comparison with delayed SCT at relapse. Two recent meta-analysis studies have shown the possibility that delayed transplantation is an equivalent option for the initial strategy of MM treatment as opposed to doing it up front. The highest profile trial addressing this question is the Intergroupe Francophone du Myélome (IFM)/Dana-Farber Cancer Institute (DFCI) 2009 study. The study randomized patients with newly diagnosed MM to receive either 8 cycles of lenalidomide, bortezomib, and dexamethasone (RVd) with stem cell collection after cycle 3 or to RVd with stem cell collection and transplantation (melphalan 200 mg/m^2) after cycle 3 followed by 2 additional cycles of RVd. Maintenance treatment with lenalidomide was given for 1 year in both arms. The complete response rate was significantly higher in the transplantation arm (59% versus 48%, $P = 0.03$) as was the rate of MRD negativity (79% versus 65%, $P < 0.001$). Median progression-free survival was significantly longer in the transplantation arm at 50 months compared to 36 months with RVd alone. Whether this translates into improved overall survival will require a longer duration of follow-up; overall survival at 4 years was almost identical in both groups at 81% and 82%, respectively. Notably, of the 172 patients in the RVd arm who developed symptomatic progression, 79% underwent salvage chemotherapy and stem cell transplantation.

Melphalan, 200 mg/m^2 (MEL200), is considered the standard myeloablative regimen for those undergoing SCT. Various clinical trials have tested other agents, such as the addition of bortezomib, previously total body irradiation, or busulfan. These trials have failed to show sufficient improvement to suggest their incorporation in clinical practice. Patients who undergo SCT usually are treated with oral cryotherapy at the time of melphalan infusion to prevent mucositis, receive prophylactic antibiotics and antivirals, and are treated with growth factors to help in the recovery of the normal bone marrow function. The procedure is associated with a low risk of treatment-related mortality of less than 1% and can be done safely in an outpatient setting, if so desired.

Tandem auto transplant refer to a planned second course of high-dose therapy and SCT within 6 months of the first course. A meta-analysis showed that patients with high-risk cytogenetics benefit more from tandem SCT (as opposed to a single SCT) and that this procedure may, at least in part, abrogate the adverse prognosis of t(4;14) and deletion 17p. However, a randomized phase 3 clinical trial (STAMINA) showed no difference in in PFS or OS in patients who received single or tandem transplants.

A second autologous SCT after first relapse can be considered in MM patients who achieve good duration of disease control with their initial transplantation. Traditionally patients who achieve disease control of at least 18 to 24 months are considered suitable candidates for repeat SCT. Given the advent of novel therapeutics that can achieve levels of disease control similar to or better than a second transplantation, subsequent SCT is a practice that will likely be diminishing.

Minimal residual disease

Detection of minimal residual disease has emerged as one of the most promising prognostic features in the care of patients with MM. The availability of better treatments has necessitated determination of residual monoclonal plasma cells at very high-resolution assays. Using multicolor flow cytometry assays, one can achieve levels of resolution as low as 1×10^{-5}. Another strategy for the detection of minimal residual disease is to use next-generation sequencing, with the identification genetic signatures (derived from the VDJ rearrangements) derived from samples at the time of diagnosis. Next-generation sequencing can lead to a level of detection of 1×10^{-6}. Both methods have been accepted at the international level and can be used for monitoring residual disease. Measurement of minimal residual disease negativity should be done only in patients suspected of having a complete or a very good partial response (VGPR).

Achieving MRD-negative status appears to be one of the most important prognostic factors for newly diagnosed MM patients. In one study, patients who achieved a complete response were further segregated into those who had MRD-negative status and those who had MRD-positive status. Those who were MRD-positive had a prognosis that was similar to that of patients who had only a partial response, and the best outcomes were seen in patients with MRD-negative status. Two meta-analyses have evaluated MRD as a prognostic marker and have concluded

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that MRD is associated with favorable clinical outcomes. Ongoing studies are evaluating the use of MRD as a clinical endpoint to provide a treatment-adapted approach to potentially discontinue therapy when MRD negativity is achieved. Clinical trial information is not yet available to answer this important question, and currently it is not recommended to make treatment decisions based on MRD status.

The United States Food and Drug Administration (FDA) has approved a next-generation sequencing assay as a validated method for MRD determination (clonoSEQ). The International Myeloma Working Group and others have also recognized the need to achieve negativity in PET scans done after stem cell transplantation (SCT).

Maintenance

The concept of continued therapy or maintenance to control the residual disease has been explored in MM for a long time. It is now accepted that maintenance therapy should be considered the standard of care for patients completing initial therapy, including SCT. Several trials tested the clinical value of using agents such as prednisone, interferon, and thalidomide as maintenance therapy, but the trials are only of historic interest for patients in the United States. For most patients lenalidomide is now recommended after SCT, at lower doses (10-15 mg) than what are used during induction.

Lenalidomide maintenance has been studied in 2 large placebo-controlled randomized trials, one conducted by the IFM and the other by the US Cancer and Leukemia Group B (CALGB) group. A significant benefit in terms of PFS has been reported for lenalidomide maintenance with respect to control arms in both trials (46 versus 27 months in the CALGB trial and 41 versus 23 months in the IFM trial), and this benefit translated into an OS advantage in the American but not in the French trial. Additionally, lenalidomide tolerability was much better than thalidomide tolerability. A meta-analysis of the data from these trials has concluded there is improvement in both PFS and OS in MM treated with lenalidomide maintenance.

Proteasome inhibitors have also been explored in the maintenance setting. Bortezomib has been tested as maintenance therapy in 2 randomized trials. In the HOVON-65 Study, patients treated with SCT were maintained with bortezomib or thalidomide, although the induction regimens were different for the 2 arms. In the PETHEMA/GEM05menos65 trial patients who received maintenance with bortezomib-thalidomide after SCT showed a significantly longer PFS (78% at 2 years) compared with those who received thalidomide (63%) or interferon (49%) alone; there were no differences in OS. The TOURMALINE-MM3 trial evaluated ixazomib versus placebo as maintenance following SCT and demonstrated an improved PFS with ixazomib (26.6 versus 21.3 months). The results of this trial, while positive, suggest lower benefit for maintenance for ixazomib versus lenalidomide. Many treatment centers have combined combinations of proteasome inhibitors (bortezomib and ixazomib) with lenalidomide in patients with high-risk disease.

Allogeneic transplantation

Several clinical trials have explored the possibility of allogeneic stem cell transplantation as therapy for MM. These clinical trials have compared both fully myeloablative conditioning regimens and the so-called mini-allogeneic approaches. The cumulative results of such trials have failed to garner enough enthusiasm among MM specialists to merit proposing allogeneic approaches as primary therapy for the disease. European studies have previously shown limited ability of allogeneic transplantation to be effective in disease control in the setting of relapsed and refractory MM. While some academic centers still consider allogeneic SCT for patients with MM under special circumstances, the vast majority of MM specialists no longer recommend it outside of clinical trials, and allogeneic SCT composes only a small minority of SCT done for MM on a yearly basis. The argument for allogeneic SCT being curative is clearly challenged in the face of excellent outcomes for MM now treated with novel agents and autologous SCT, where a small minority of patients can be cured.

Treatment of transplantation-ineligible patients

The combination of melphalan and prednisone (MP) was studied extensively in the nontransplantation MM population beginning in the 1960s and was the standard therapy until the advent of the new drugs. Overall response rates from different studies varied from 40% to 60% (CRs were rare), and median overall survival was around 3 years. With the introduction of the new drugs, a series of phase 3 trials was undertaken examining the impact of adding thalidomide, lenalidomide, or bortezomib to MP in this population. While traditionally patients ineligible for transplantation were predominantly treated with these melphalan-based regimens, novel non-melphalan-containing regimens, developed for patients prior to undergoing stem cell transplantation, are now the standard as initial treatment in transplantation-ineligible patients as well.

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Daratumumab-based regimens

The phase 3 MAIA trial included 737 newly diagnosed, transplant-ineligible MM in a randomized trial evaluating lenalidomide/dexamethasone with or without daratumumab to evaluate PFS as the primary endpoint. After a median follow-up of 56.2 months, the mPFS was not reached in the daratumumab group versus 34.4 months in the control group. Further, the triplet combination resulted in a significant improvement in overall survival with a 32% reduction in the risk of death as well (5-y OS 66.3% versus 53.1%; hazard ratio [HR], 0.68; $P = 0.013$). Toxicity of the triplet combination included grade 3 or higher neutropenia in 54% of patients. No other new safety concerns were noted with longer term follow-up.

Although melphalan is rarely used now in the United States a trial is notable. In 2018, results were published from the randomized phase 3 ALCYONE trial of the CD38 antibody daratumumab in combination with bortezomib, melphalan and prednisone (VMP) (Dara-VMP) versus VMP alone in newly diagnosed myeloma patients ineligible for transplantation. A total of 706 patients in both arms received VMP for nine 6-week cycles. In the daratumumab arm, patients received 16 mg/kg of daratumumab once weekly for 6 weeks (cycle 1), followed by once every 3 weeks (cycles 2-9), and then every 4 weeks until progression. The addition of daratumumab (Dara-VMP) resulted in higher response rates (overall response rate [ORR] 91% and CR 43% versus ORR 74% and CR 24%) as well as 3-fold higher rates of MRD negativity (22% versus 6%). Treatment with daratumumab +VMP reduced the risk of death or progression by 50% compared to VMP alone; the median PFS for daratumumab-VMP was not reached compared to 18.1 months for patients who did not receive daratumumab.

The MAIA and ALCYONE randomized phase 3 studies show the superior clinical efficacy and improvement in overall survival with daratumumab in combination with standard of care regimens versus standard of care alone for transplant-ineligible patients with newly diagnosed MM and present a new standard of care option.

Lenalidomide-dexamethasone versus bortezomib-lenalidomide-dexamethasone

In a phase 3 study performed by the Southwest Oncology Group (SWOG 0777), 471 patients without immediate plan for autologous stem cell transplantation were randomized to receive lenalidomide-dexamethasone (Rd) or bortezomib-lenalidomide-dexamethasone, both followed by lenalidomide maintenance. Rd was given for six 28-day cycles consisting of lenalidomide 25 mg on days 1-21 and weekly dexamethasone 40 mg. VRd consisted of eight 21-day cycles of intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11, lenalidomide 25 mg on days 1-14, and dexamethasone 20 mg on the days of, and days after, bortezomib. The overall response rate was 82% in the VRd arm and 72% in the Rd arm. Adding bortezomib to Rd therapy resulted in a significantly improved median progression-free survival of 43 versus 30 months in the Rd group. Importantly, median overall survival was 75 months for VRd versus 64 months for Rd. Adverse events of grade 3 or higher were reported in 82% of patients in the VRd group and 75% of patients in the Rd group. These results support the use of RVd as standard of care for older patients with myeloma, though only 43% of patients in the study were aged 65 years or older.

Modifications of the dosing used with this combination have been proposed for the frail patients and those of very advanced age or with significant comorbidities.

Carfilzomib or ixazomib plus alkylators

Second-generation proteasome inhibitors in combination with alkylators are also being considered as therapeutic options for newly diagnosed nontransplantation-eligible MM patients. In a pilot phase 1/2 trial, carfilzomib combined with MP (KMP) demonstrated promising efficacy results (ORR of 90% and rate of VGPR or better of 58%) with an acceptable toxicity profile with no grade 3-4 peripheral neuropathy (PN), and provided the rationale for a randomized trial comparing KMP with VMP. Early results of the CLARION trial, however, showed no difference in median PFS (22.3 months for KMP versus 22.1 months for VMP). Furthermore, the rate of fatal treatment-emergent adverse events was higher with carfilzomib compared to bortezomib suggesting that carfilzomib-MP is not a preferred option for older patients, at least not in combination with MP. The combination of carfilzomib (up to 36 mg/m^2 twice weekly) plus cyclophosphamide and dexamethasone (KCD) was evaluated in a series of 58 newly diagnosed older MM patients and showed an ORR rate of 95%, including a CR rate of 33% and a stringent CR rate of 20%. No grade 3-4 PN was reported and tolerability was good, though 7% of patients experienced cardiopulmonary toxicity. In a follow-up study of KCD on a weekly schedule, the carfilzomib dose was increased up to 70 mg/m^2 and similarly high response rates were achieved translating into 2-year progression-free and overall survivals of 53.2% and 81%, respectively. Carfilzomib has also been combined with lenalidomide-dexamethasone (KRd) in a pilot phase 1/2 trial in newly diagnosed young and older MM patients. Results of a subanalysis of 23 older MM patients showed impressive efficacy (100% of ORR, with stringent CR in 65% of patients), and an acceptable

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toxicity profile (13% grade 1-2 PN). All patients remained free of progression and alive at the median follow-up of 1 year. These results support a phase 3 study of KRd versus Rd in all age groups.

Ixazomib (MLN9708), an oral second-generation proteasome inhibitor FDA-approved in 2015, plus MP in a biweekly or weekly scheme is also currently undergoing a phase 1/2 clinical trial to evaluate the efficacy and safety of this combination. Lenalidomide-dexamethasone alone is being also compared with lenalidomide-dexamethasone plus ixazomib in a randomized trial in non-transplantation-candidate MM patients supported by the positive preliminary results showed with ixazomib given weekly plus lenalidomide-dexamethasone (92% of patients achieved at least PR, including a VGPR or better rate of 58% and a CR rate of 27%) with good tolerability.

Maintenance therapy in older patients

The role of lenalidomide maintenance in this patient population, following initial therapy with MPR (MP plus lenalidomide), was evaluated in the MM-015 study. PFS was significantly improved in the MPR-R group compared with the MPR group, with no difference in OS. There was increased hematological toxicity with addition of lenalidomide, and there was also an increased incidence of second primary malignancies with the use of lenalidomide maintenance. The FIRST trial that compared continuous lenalidomide-dexamethasone until progression with fixed-time lenalidomide-dexamethasone (18 cycles) showed a longer PFS for continuous treatment (25.5 versus 20.7 months; HR, 0.70; $P = 0.0001$) with no differences in OS (59.4% versus 55.7% at 4 years). Finally, second-generation proteasome inhibitors are being evaluated as part of consolidation therapy (carfilzomib in a modified schedule) or maintenance therapy (carfilzomib and ixazomib weekly until disease progression), preliminary data indicate that both, carfilzomib and ixazomib upgrade the depth of response.

Individualizing treatment of older patients

The previously mentioned novel treatment combinations offer physicians the possibility of tailoring treatment approaches by taking an individual patient's profile and preferences into account. Physicians should undertake 2 actions before prescribing treatment for older patients: (1) assess the patient's biological age, comorbidities, frailty, and disability in order to select the most appropriate drug regimen, adapting the dose if required (Table 25-11); and (2) optimize the supportive care treatment with bisphosphonates, antibiotics, antivirals, anticoagulants, growth factors, physical therapy, and pain control.

For unfit older patients, dose adjustments are key to improving tolerability. Bortezomib should always be given in a weekly scheme and as a subcutaneous formulation in combination with low-dose steroids (sometimes prednisone may be better tolerated than dexamethasone). Oral drugs can be more convenient for frail older patients; lenalidomide can be given at a low or standard dose with low-dose dexamethasone.

Other factors should be considered when making treatment decisions. In patients who have a history of venous thromboembolism (VTE), avoidance of an immunomodulatory agent may be desired, but, if not possible, more aggressive preventive measures are needed. Appropriate anticoagulant prophylaxis has been shown to reduce VTE

Table 25-11 Recommended dose modifications for functional impairment in older patients

Agent	Dose level 0	Dose level 1	Dose level 2
Bortezomib	1.3 mg/m^2 twice/wk	1.3 mg/m^2 once/wk	1.0 mg/m^2 once/wk
	d 1, 4, 8, 11 / 3 wk	d 1, 8, 15, 22 / 5 wk	d 1, 8, 15, 22 / 5 wk
Lenalidomide	25 mg/d	15 mg/d	10 mg/d
	d 1-21 / 4 wk	d 1-21 / 4 wk	d 1-21 / 4 wk
Dexamethasone	40 mg/d	20 mg/d	10 mg/d
	d 1, 8, 15, 22 / 4 wk	d 1, 8, 15, 22 / 4 wk	d 1, 8, 15, 22 / 4 wk
Melphalan	0.25 mg/kg (9 mg/m^2)	0.18 mg/kg (7.5 mg/m^2)	0.13 mg/kg (5 mg/m^2)
	d 1-4 / 4-6 wk	d 1-4 / 4-6 wk	d 1-4 / 4-6 wk
Prednisone	50 mg every other day	25 mg every other day	12.5 mg every other day
Cyclophosphamide	100 mg/d	50 mg/d	50 mg every other day
	d 1-21 / 4 wk	d 1-21 / 4 wk	d 1-21 / 4 wk

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complications to approximately 3% in patients treated with immunomodulator-containing regimens. In patients with preexisting neuropathy, Rd would be a good choice for up-front treatment because lenalidomide is only infrequently associated with neurotoxicity; similarly, carfilzomib has a low risk of PN. In patients with renal failure, bortezomib, thalidomide, and steroids can be administered at the full approved dose and dose-adjusted lenalidomide can be considered. Geriatric assessment tools also offer an opportunity for objective frailty assessments to help guide clinical recommendations.

Treatment of relapsed MM

With the current treatments, the vast majority of patients with MM will eventually relapse, and therapy will have to be reinstituted or changed. The choice of regimens at the time of relapse depends on a variety of factors as outlined in Table 25-12, especially the type of relapse, efficacy and toxicity of previous therapies, and available treatment options. The timing of initiation of therapy has to be carefully considered. As with initial therapy, it has to be guided by the clinical scenario.

Patients, especially after SCT, can have a slow biochemical progression with no clear end-organ damage, a situation akin to MGUS and SMM, where expectant observation may be the appropriate step. However, in patients who present with significant complications of clinical relapse, such as neurological complications and renal failure, earlier intervention may be warranted. Clinical trials should always be considered in patients with relapsed disease. Most of the up-front combinations that have been studied can also be used in the relapsed setting, based on the prior use of the specific drugs and the presence of toxicities.

It is important to separate younger and more fit patients from older patients with relapsed MM. In young patients relapsing after transplantation, one can consider the timing of relapse and the aggressiveness of the disease. If the relapse occurs within the first year after transplantation, patients should be immediately considered high-risk and, in order to overcome drug resistance, should be treated with multidrug combinations incorporating novel agents or on a clinical trial. If relapse occurs 1 to 3 years after autologous SCT, many investigators would favor rescue with novel agents starting with a new line of treatment and shifting to the second and subsequent lines only when disease progression occurs. Finally, if relapse occurs more than 3 years after the first autologous SCT, an attractive possibility is reinduction with the initial treatment or other novel-agent combination followed by a second autologous SCT.

For older patients, treatment decisions at relapse must take into account the general condition of the patient. Once the patient relapses after up-front treatment, the durations of subsequent responses to rescue therapies are progressively shortened. Therefore, the current goal in relapsed MM is to optimize the efficacy of novel drugs through their most appropriate combinations, to establish optimal sequences of treatment, and to promote active clinical research on experimental agents that have already shown promising activity in in-vitro and animal models.

The management of relapsed MM can broadly be categorized as early or late relapse, based on the number of prior lines of therapy received.

Table 25-12 Considerations for choosing treatment for relapsed MM

Presence of end-organ damage from the relapsed disease
Drugs used before, the responses observed, and the time elapsed from prior exposure
Prior use of SCT in those eligible for the procedure
Residual toxicity from prior therapy
Bone marrow and organ function
Duration of initial response
Presence of high-risk chromosome abnormalities
Age and functional status
Goals and preferences of the patient

Triplet combinations

The modern treatment of relapsing MM has been based on the principle that more effective disease control can be achieved with the use of triplet combinations. In some unique clinical situations, doublet combinations can be considered, but most recent clinical trials have shown superiority of triplet combinations. Table 25-13 shows the response rates and PFS for the various triplet combinations of recently approved combinations. While we discuss these agents separately in the following, it is important to remark that, in the majority of cases, triplet combinations should be considered the standard of care. Exceptions to this statement might include patients with poor tolerance or the occasional individual with extraordinary responses to doublet therapy.

Agents used in early relapse

Monoclonal antibodies

Monoclonal antibody therapy has seen resounding success in plasma cell disorders Elotuzumab is a humanized monoclonal IgG1 antibody targeting human CS1

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Table 25-13 Randomized phase 3 trials for relapsed/refractory multiple myeloma

	KRd (vs Rd) (ASPIRE)	EloRd (vs Rd) (ELOQUENT-2)	DaraRd (vs Rd) (POLLUX)	DaraVd (vs Vd) (CASTOR)	DaraKd (vs Kd) CANDOR	IsaPd (vs Pd) ICARIA	SeliVd (vs Vd) BOSTON
ORR	87%	79%	93%	83%	84%	63%	76%
≥VGPR	70%	33%	76%	59%	69%	49%	-
CR	32%	4%	43%	19%	29%	5%	7%
DOR, mo	28.6	20.7	NR	NR	NR	13.5	20.3
PFS, mo	26.3 (vs 17.6)	19.4 (vs 14.9)	NR (vs 18.4)	NR (vs 7.2)	NR (vs 16)	11.5 (vs 6.5)	14 (vs 9.6)

(SLAMF7), a cell-surface glycoprotein. SLAMF7 is highly and uniformly expressed on MM cells, with limited expression on natural killer cells and $CD8^+$ cells and little to no expression in normal tissues. Early phase studies have shown that, while elotuzumab has no single-agent activity, it is active in combination with bortezomib and immunomodulatory agents.

Daratumumab is a fully human IgG1-k monoclonal antibody that is directed against CD38, a cell-surface marker that is highly expressed on plasma cells. In the SIRIUS trial, that included 112 heavily pretreated and double-refractory MM patients, single-agent daratumumab induced a 29% RR, with a duration of response (DOR) of 7.4 months and a PFS of 3.7 months. These positive results prompted the investigation of the use of daratumumab in a variety of combinations which are reviewed in the following. A subcutaneous formulation of daratumumab was compared to the intravenous preparation in a noninferiority study (COLUMBA) which confirmed similar efficacy with improved safety due to fewer infusion-related reactions.

Isatuximab is a chimeric IgG1-k anti-CD38 monoclonal antibody approved in relapsed/refractory multiple myeloma in several combinations and will be reviewed in the following.

All monoclonal antibodies generally offer a safe treatment option with similar toxicity profiles when anti-CD38 was added to standard regimens. Common toxicities include infusion-related reactions, drug-induced cytopenias and increased risk of infections.

Lenalidomide

The use of prolonged maintenance therapy after initial induction with lenalidomide-based combinations, often results in lenalidomide-refractory disease at the time of relapse. For the occasional patient who did not receive prolonged lenalidomide-based therapy, it can be reinitiated in a variety of combinations during early relapse. Recent studies have shown excellent results when lenalidomide-dexamethasone is combined with second-generation proteasome inhibitors or monoclonal antibodies. A phase 3 trial (ASPIRE) compared the efficacy of carfilzomib with lenalidomide-dexamethasone versus the standard lenalidomide- dexamethasone regimen (KRd versus Rd) in 792 patients with relapsed myeloma. KRd was associated with a significantly longer median PFS (26.3 versus 17.6 months) and OS (HR, 0.79), as well as higher RR including 31.8% CR versus 9.3% CR in the control arm. The use of lenalidomide in combination with monoclonal antibodies in early relapse included combinations with elotuzumab and daratumumab. A recent phase 3 trial (ELOQUENT-2) randomized 646 relapsed/refractory patients, who had already been treated with 1-3 lines of therapy, to receive lenalidomide-dexamethasone with or without elotuzumab (10 mg/kg); the triplet combination was associated with a slightly higher RR (79% versus 66%) and a longer median PFS (19.4 versus 14.9 months). In a recent phase 3 study (POLLUX), 569 myeloma patients who had received at least 1 therapy were randomly assigned to receive lenalidomide-dexamethasone with or without daratumumab. Significantly more patients assigned to daratumumab responded to treatment (92.9% versus 76.4%), $P < 0.001$) and achieved a better CR (43.1% versus 19.2%) and MRD negativity (22.4% versus 4.6%). These results translated into improved progression-free survival at 12 months which was 83.2% for the triplet compared to 60.1% for lenalidomide-dexamethasone.

Pomalidomide

Pomalidomide is another immunomodulatory drug that has been approved for treatment of relapsed or refractory myeloma, and has activity in lenalidomide-refractory patients. Pomalidomide has been evaluated in a variety of combinations for relapsed disease. The ELOQUENT-3 study demonstrated an improvement in mPFS with the addition of the anti-SLAMF7 monoclonal antibody elotuzumab to pomalidomide/dexamethasone (10.3 versus 4.7 months). Improved PFS was also noted in the triplet combination of pomalidomide/bortezomib/dexamethasone when compared to bortezomib/dexamethasone (11.2 versus 7.1 months). Results of the combination of

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pomalidomide/dexamethasone with or without daratumumab (APOLLO) and pomalidomide, dexamethasone with or without isatuximab (ICARIA) have both shown significant improvement of outcomes with the monoclonal antibody. The APOLLO study showed an improved PFS with median 12.4 versus 6.9 months in patients with median 2 prior lines of therapy, nearly 80% of which were refractory to lenalidomide. ICARIA included patients with median 3 prior lines of therapy and showed an improvement in median PFS of 11.5 versus 6.5 months in isatuximab/pomalidomide/dex arm.

Bortezomib

Patients who receive bortezomib during induction therapy often retain sensitivity to the drug due to a preplanned discontinuation of the drug to minimize toxicity. This provides an opportunity to reuse the drug during early relapse. Single-agent response rates in relapsed/refractory myeloma range from 28% to 38% with a median DOR of 8 months. The CASTOR trial randomized 498 relapsed or refractory patients to receive either daratumumab in combination with bortezomib-dexamethasone or bortezomib-dexamethasone alone. The addition of daratumumab resulted in improved overall response rates (83% versus 63%) and doubled rates of CR or better (19% versus 9%) and VGPR or better (59% versus 29%). Median progression-free survival in the 2 groups was not reached compared to 7.2 months (HR, 0.39; 95% CI, 0.28-0.53). In a smaller phase 2 study, 152 patients with relapsed myeloma, who had received 1 to 3 therapies, were randomized to receive elotuzumab-bortezomib-dexamethasone (EBd) or bortezomib-dexamethasone (Bd). While the ORRs were similar at 66% for EBd and 63% for Bd, the median PFS was longer in the elotuzumab group at 9.7 months compared to 6.9 months in the control arm.

Carfilzomib

Carfilzomib (K) is a next-generation selective proteasome inhibitor that has been approved for treatment of relapsed MM. Initial phase 2 studies gave carfilzomib 20 mg/m^2 intravenously twice weekly for 3 of 4 weeks in cycle 1 followed by 27 mg/m^2 on the same schedule during subsequent cycles. This regimen resulted in overall response rates of approximately 20% in a population of predominantly bortezomib-refractory patients (PX-171-003-A1), and 60% in relapsed, bortezomib-naïve patients. Common toxicities encountered were fatigue, anemia, nausea, and thrombocytopenia. There is less neuropathy with carfilzomib compared to other proteasome inhibitors, but cardiac adverse events have been described in up to 18% of patients including hypertension, heart failure, and arrhythmia. Carfilzomib has been evaluated in combination with both approved anti-CD38 monoclonal antibodies. The CANDOR study was a phase 3 trial comparing the carfilzomib doublet with or without daratumumab, with twice weekly carfilzomib dosing. Median PFS was not reached (NR) and 15.8 months for DKd and Kd, respectively, with a 37% reduction in the risk of progression or death (HR, 0.63; $P = 0.0027$) for the triplet arm. The subsequent PLEIADES study evaluated the same triplet combination with subcutaneous daratumumab with similar high response rates. The addition of isatuximab to carfilzomib/dexamethasone was also evaluated in a phase 3 randomized study (IKEMA), demonstrating high overall response rates (87 versus 83%) in both arms, with mPFS (NR versus 19.2) showing the benefit in the triple arm.

Ixazomib

Ixazomib is an oral proteasome inhibitor that was approved by the FDA in 2015. In combination with dexamethasone, ixazomib has a response rate of 43% in patients with relapsed myeloma not refractory to bortezomib. The Tourmaline study randomized 722 patients with relapsed or refractory myeloma, who had received 1 to 3 prior therapies, to lenalidomide-dexamethasone plus ixazomib/placebo. More patients in the ixazomib group responded to treatment (ORR 78% versus 72%), and improved median PFS was observed (20.6 versus 14.7 months). Ixazomib is also being evaluated in combination with other agents, such as cyclophosphamide or pomalidomide.

Selinexor

Exportin 1 (XPO1) is a protein that transports glucocorticoid receptor- and tumor-suppressor proteins out of the nucleus, effectively resulting in their inactivation. Selinexor is an orally bioavailable agent that specifically blocks exportin 1, allowing nuclear retention of glucocorticoid receptor and tumor-suppressor proteins to exert their antioncogenic function. The phase 2 STORM study evaluated selinexor in combination with dexamethasone in highly refractory patients (refractoriness to lenalidomide, pomalidomide, bortezomib, and carfilzomib is considered quad-refractory; or penta-refractory after additional treatment with daratumumab). Encouraging overall response rates of 21% and 20% were reported in quad- and penta-refractory patients, respectively. The most common toxicities were nausea, fatigue, anorexia, and vomiting, as well as cytopenias. Bortezomib/dexamethasone, with or without selinexor, was evaluated in the phase 3 open-label BOSTON trial in patients with 1-3 prior lines of therapy.,

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The trial showed an improved ORR in the triplet arm relative to the doublet (76% versus 62%) with mPFS 14 versus 9 months, respectively. This led to the approval of selinexor/bortezomib/dexamethasone for the relapsed/refractory MM (RRMM) with at least 1 prior line of therapy. Trials evaluating additional combinations with selinexor are underway.

Late relapse

B-cell maturation antigen (BCMA) is widely expressed on MM cells and is an attractive target for antimyeloma therapy. Belantamab mafodotin is the first-in-class antibody drug conjugate for the treatment of relapsed refractory MM. It is an anti-BCMA antibody drug conjugate composed of humanized IgG1 anti-BCMA Mab conjugated via a linker with mafodotin, a potent microtubule inhibitor, which leads to cell cycle arrest within the myeloma cell. The phase 1 dose escalation and expansion trial (DREAMM-1) showed an overall response rate of 60% and mPFS 12 months in highly refractory patients with a median 5 prior lines of therapy. The DREAMM-2 study was a two-arm phase 2 trial evaluating 2 different doses, 2.5 mg/kg and 3.4 mg/kg, showing a mPFS of 2.9 and 4.9 months, respectively. Ocular toxicity was common as 70% of patients developed keratopathy, with higher rates in the 3.4 mg/kg arm overall prompting the FDA approval of the drug at 2.5 mg/kg dose level. All events were reversible with no permanent loss of vision, but did require dose reduction or delays. Based on this single-agent activity, several other studies are now evaluating the combination of belantamab mafodotin with various agents in combination.

Chimeric antigen receptors (CARs) are engineered receptors that allow redirection of autologous effector immune T cells to a specific target. B-cell maturation antigen is widely expressed on MM cells and is an attractive target for CAR T-cell technology. Idecabtagene vicleucel (ide-cel) is the first CAR approved for the treatment of relapsed/refractory MM. Its approval was based on the KARMMA phase 2 study which evaluated escalating doses of CAR T-cells after lymphodepleting chemotherapy. Of the 140 patients with at least 3 prior regimens including a PI, immunomodulatory and anti-CD38 Mab enrolled, 128 received ide-cel and after a median follow-up of 13.3 months, 73% had a response to therapy, and 33% had a complete or stringent complete response. Responses were dose dependent with patients receiving 450×10^6 CAR T cells having the highest response (81%). The mPFS was 8.8 months overall, and 20.2 months in patients who achieved a CR or sCR. Median OS was 19.4 months but was immature at time of publication. Multiple other CAR constructs and T-cell engagers with various targeted antigens are currently undergoing investigation.

Other novel agents for relapsed or refractory disease

In lymphoid malignancies, overexpression of the antiapoptotic B-cell lymphoma-2 (Bcl-2) protein has been shown to confer resistance to chemotherapy. Venetoclax blocks Bcl-2 and induces cell death of myeloma cells, especially those with the t(11;14) translocation overexpressing Bcl-2. In a phase 1 study of single-agent venetoclax in 66 heavily pretreated patients, an ORR of 21% was reported for the overall cohort, but 86% of patients with t(11;14) responded. Common adverse events included mild gastrointestinal symptoms (nausea 47%, diarrhea 36%, vomiting 21%) and cytopenias. Based on preclinical studies showing that venetoclax enhanced bortezomib activity, the 2 agents were combined in a phase 1b study of 66 previously treated myeloma patients including 39% refractory to bortezomib. The ORR for all patients was 67%, but response rates as high as 97% and VGPR or better of 73% were observed in patients not refractory to bortezomib who had received 13 prior treatments. Median time to progression and DORs were 9.5 and 7 months, respectively.

Management of high-risk myeloma and risk-adapted therapy

With MM, similar to other hematologic malignancies, specific variables have been recognized to influence prognosis; these include patient characteristics, International Staging System (ISS) stage, disease biology, and treatment response. There are 3 main patient characteristics that influence survival: age, comorbidities (renal failure, cardiac failure, etc.), and performance status/frailty. Disease-related risk factors are mainly represented by cytogenetic/FISH abnormalities [t(4;14), 17p deletion, t(14;16), t(14;20), +1q and complex karyotype] and molecular signatures that are associated with outcome. In addition, there are many factors related to tumor burden, including low serum albumin, high β_2-microglobulin or LDH, high number of circulating PCs, and extramedullary disease. Furthermore, resistance to therapy is a major determinant of prognosis (refractory disease, early relapse, or suboptimal response). There is no unified definition of high risk myeloma, but generally patients are considered high risk if they belong to the following subgroups: (i) patients with t(14;16), t(14;20), or del17p13; (ii) patients with elevated LDH; (iii) patients with a high number of circulating plasma cells; (iv) patients with high-risk signature on gene-expression profiling; and (v) patients who fail to achieve at least a PR

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to optimized induction therapy. The expected survival of these patients is usually less than 3 years.

Choice of therapy in high-risk myeloma patients

The concept of high-risk cytogenetics emerged from data using induction therapy with conventional chemotherapy followed by SCT, showing a 20% to 50% decrease in OS for high- as compared to standard-risk patients. The first novel drug tested was thalidomide used as either induction or maintenance therapy, and again high-risk patients did significantly poorer than standard-risk patients. Moreover, studies derived from the UK group (MRC IX intensive, MRC IX nonintensive, MRC IX maintenance) indicate that thalidomide is not superior to conventional chemotherapy in patients with high-risk cytogenetic abnormalities. Regarding lenalidomide, a small study conducted by Kapoor et al in newly diagnosed patients showed that high-risk patients display significantly shorter PFS (18 versus 36 months, for high- versus standard risk, respectively). In the lenalidomide-dexamethasone (high- versus low-dose) trial the 2-year OS was also significantly shorter for high-risk patients (76% versus 91%). THE IFM group has shown that lenalidomide maintenance may be of some benefit in patients with deletion 17p (PFS: 29 versus 14 months). Nevertheless, it should be noted that these PFS values are clearly inferior to those of the overall series of patients (42 months). Therefore, it could be concluded that lenalidomide maintenance improves the outcome especially in patients with del (17p) but does not completely overcome the poor prognosis of high-risk cytogenetics.

There are now strong data that demonstrate that the poor prognosis associated with chromosomal translocation (4;14) may be improved by the addition of bortezomib as part of induction and consolidation in newly diagnosed transplantation-eligible patients. A meta-analysis of 3 European trials confirms a benefit from a bortezomib-based regimen in patients with high-risk cytogenetics, especially translocation (4;14) and deletion 17p because this improves outcome although does not completely overcome adverse prognosis of these abnormalities, particularly deletion 17p. In transplantation-ineligible patients with high-risk MM, the Spanish GEM-05 trial that included bortezomib-melphalan-prednisone versus bortezomib-thalidomide-prednisone induction revealed shorter PFS/OS for high-risk MM. Therefore, the first-generation novel agents may have improved, but certainly did not overcome, the adverse prognosis of high-risk MM.

The data with the second-generation novel agents carfilzomib and pomalidomide is primarily in the RRMM setting. In the pivotal phase 2 trial that led to the approval of carfilzomib, patients with isolated translocation (4;14) had a remarkably high ORR 63.6% with a median PFS of 4.1 months and OS of 15.8 months suggesting that this group did as well as the standard-risk group. These results may reflect a class effect because bortezomib also benefits the t(4;14) MM. Carfilzomib, however, did not improve the poor outcome of deletion17p either by itself or in combination with other abnormalities. The MM-003 phase 3 trial, as well as an IFM phase 2 study, showed that pomalidomide plus low-dose dexamethasone might provide a comparable survival benefit to deletion 17p RRMM patients (12.6 months versus 14 months for patients without deletion 17p). However, patients with the t(4;14) did not appear to derive the same benefit from pomalidomide.

The experience with combinations of proteasome inhibitors and immunomodulators is limited but might prove beneficial. In an effort to avoid alkylator-based therapy that could potentially accelerate clonal evolution, a study evaluating the use of RVd consolidation and maintenance following high dose therapy (HDT) showed significantly improved PFS and OS for high-risk patients. In the relapsed setting, the combination of carfilzomib, pomalidomide, and dexamethasone demonstrated high response rates of 78% in patients with high-risk cytogenetics compared to 74% in standard-risk patients suggesting that this combination may add significant benefit.

Regarding ASCT, Cavo et al, in a meta-analysis of 3 European phase 3 trials has shown that patients with high-risk cytogenetics who failed to achieve CR after bortezomib-based induction did significantly better with tandem autologous stem cell transplantation, with a doubling of PFS (42 versus 21 months, $P = 0.004$) and 4-year OS (76% versus 33%, $P = 0.0001$) as compared with single ASCT. Of note, the reported experience is not based on randomization, and different maintenance regimens were used. Nevertheless, the observation that the greatest benefit of tandem transplantation was observed in high-risk patients who did not achieve a CR with induction illustrates the importance of achieving a CR in this population. Although some data suggest that high-risk patients may benefit from allogeneic stem cell transplantation, the data correspond to small selected series of patients. In a larger study comparing tandem autologous transplantation versus autologous transplantation followed by allogeneic transplantation, no benefit for the high-risk group was observed.

The SWOG-1211 randomized phase 2 trial comparing 8 cycles of VRd with or without elotuzumab is the sole available randomized study in newly diagnosed high-risk MM. Interesting efforts for patients with high-risk disease,

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especially in the newly diagnosed setting, will include the incorporation of other monoclonal antibodies and immune-based strategies. In addition, the development of agents targeting the specific genetic abnormality, such as FGFR3 or MMSET, may prove to be beneficial.

Supportive care

Bone disease: assessment and treatment

Bone involvement is the most frequent clinical complication in patients with MM. About 70% of patients have lytic bone lesions with or without osteoporosis, and another 20% have osteoporosis without lytic lesions. These frequencies correspond to results obtained from conventional skeletal radiography assessment, a technique that is associated with low sensitivity. CT has the highest sensitivity for the detection of bone defects and, with the whole-body low-dose modality, the radiation exposure is much lower than with conventional CT; the scanning time is short, and CT has now replaced conventional X-ray. MRI has the highest resolution for soft tissue and bone marrow infiltration; it is particularly valuable for differentiation between benign and malignant fractures but is inferior to CT for assessment of bone disease. Finally, PET allows assessment of tumor metabolism and disease activity (versus inactive or necrosis) and may be of prognostic significance.

The intravenous agents pamidronate and zoledronic acid have a long track record of clinical benefit in the treatment of bone disease in patients with MM. IMWG consensus recommendations state that bisphosphonates should be administered to all patients with active multiple myeloma, regardless of the presence or absence of multiple myeloma-related bone disease on imaging studies. Zoledronic acid is the preferred bisphosphonate due to a significant reduction in the mortality rate in randomized trials. Bisphosphonates should be administered monthly for at least 12 months and if a very good partial response or better is achieved, the dosing frequency can be adjusted or the drug discontinued. Receptor activator of nuclear factor κB ligand (RANK-L) activates osteoclasts which are critical for bone resorption. The monoclonal antibody denosumab inhibits RANK-L and thereby protects bone from degradation. In a randomized, placebo-controlled, phase 3 noninferiority study, a total of 1718 patients with newly diagnosed myeloma received either subcutaneous denosumab or intravenous zoledronic acid. The median time to the first skeletal-related event, approximately 23 months, was nearly identical for the 2 arms. The most common adverse events in the denosumab arm were diarrhea (33.5%) and nausea (31.5%). Denosumab is not cleared by the kidneys and represents a new option for bone protection in myeloma, especially for patients with renal insufficiency. Osteonecrosis of the jaw is a well-known complication of bisphosphonate therapy and preventive measures are effective in reducing its incidence. A randomized trial comparing teriparatide, an osteoanabolic agent that improves bone healing, to placebo demonstrated a greater resolution of ONJ in the treatment arm (45.4% versus 33.3%; $P = 0.013$). In relapsed patients, treatment with bisphosphonates can be restarted and administered concomitantly with active therapy.

Between 15% and 20% of patients with MM have hypercalcemia at the time of diagnosis. A common complication of hypercalcemia is renal impairment caused by interstitial nephritis. Treatment of hypercalcemia with hydration, steroids, and bisphosphonates is a medical emergency. Zoledronic acid is the bisphosphonate of choice due to its quicker response and significantly longer time to recurrence compared with pamidronate. Calcitonin can be used in patients who are refractory to bisphosphonates.

Some patients develop pathological fractures of long bones and require orthopedic surgery. In the event of extensive lesions, stabilization surgery can be followed by local radiation therapy. Prophylactic orthopedic intervention should be considered in patients with large lytic lesions in weight-bearing bones at high risk of fracture. Patients with severe back pain due to vertebral compression fractures can benefit from vertebroplasty or kyphoplasty. Spinal cord compression caused by a vertebral fracture is very rare in patients with MM. This complication instead is usually caused by a plasmacytoma arising from a vertebral body, and management is described further in the following.

Anemia and bone marrow failure

Approximately 35% of patients with newly diagnosed MM have a hemoglobin level lower than 9 g/dL. In addition, severe anemia is a frequent complication later in the course of the disease due to disease progression. Anemia is associated with a significant loss in quality of life and a poor prognosis. The main causes of anemia in MM are bone marrow replacement by PCs, relative erythropoietin deficiency, renal insufficiency, and chemotherapy with cytotoxic agents. Severe neutropenia and thrombocytopenia at the time of diagnosis are unusual. About 10% of patients have a platelet count of $<100 \times 10^9$/L, but platelet counts lower than 20×10^9/L, with risk of severe bleeding, are unusual.

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A number of trials have shown the beneficial effect of recombinant human erythropoietin and darbepoetin alfa in the treatment of myeloma-associated anemia. Hemoglobin levels above 12 g/dL should be avoided due to association with a higher risk of thrombosis and poorer outcomes. The major cause of erythropoietin failure is iron deficiency. Iron repletion should be initiated when there is evidence of true or functional iron deficiency. Treatment with granulocyte colony-stimulating factor (G-CSF) may be required for chemotherapy-induced severe granulocytopenia. Patients treated with lenalidomide may require G-CSF therapy, but dose reduction or selection of an alternate agent is usually a better strategy.

Renal failure

About 20% of patients with MM have a serum creatinine level higher than 2 mg/dL at diagnosis. However, in some series, up to 10% of patients with newly diagnosed MM have renal failure severe enough to require dialysis from the time of diagnosis. The main causes of renal failure in MM patients are light-chain excretion resulting in cast nephropathy (myeloma kidney) and glomerular deposition of Ig (light-chain amyloidosis or immunoglobulin deposition disease). Other causes include hypercalcemia, the use of nephrotoxic agents (NSAIDs or contrast dye), and, rarely, hyperuricemia. The prognosis mainly depends on the reversibility of renal dysfunction. The median survival of patients with reversible renal failure is similar to that of patients with normal renal function, whereas patients with nonreversible renal failure have a median survival of fewer than 12 months.

Unless contraindicated, intravenous fluids are used to decrease light-chain concentration in the tubular lumen and treat potential hypovolemia or hypercalcemia. Because the action of bortezomib is very quick, it is the ideal agent for rapidly decreasing paraprotein levels to prevent the development of irreversible renal failure by avoiding further tubular light-chain damage. In a retrospective series of 24 patients with relapsed/refractory MM and dialysis-dependent renal failure, the overall response rate was 75%, with 30% CR or near-complete remission. Subsequent studies have confirmed the benefit of bortezomib-based therapies (in combination with dexamethasone with or without doxorubicin or immunomodulators) in patients with newly diagnosed myeloma and renal failure. Steroids and thalidomide can also be used at full dose in patients with renal failure, whereas the doses of lenalidomide and pomalidomide must be adjusted to the degree of renal failure. Based on pharmacokinetic analysis, dose reduction is not required for monoclonal antibodies, such as daratumumab, in patients with reduced creatinine clearance of 30 to 60 cm^3/minute, and first reports suggest safety in patients on dialysis.

With regard to the use of high-dose therapy/autologous stem cell transplantation in patients with MM and renal failure, the largest experience comes from a CIBMTR retrospective analysis including 252 patients with moderate or severe renal insufficiency. This review demonstrated that high-dose melphalan and SCT is safe in patients with moderate and severe renal insufficiency at the time of transplant. Five-year PFS improvements (46% versus 18%, $P = 0.009$) were noted in patients with moderate renal insufficiency (30-60 mL/min) who received melphalan 200 mg/m^2 when compared to 140 mg/m^2, but was not seen in those with severe renal insufficiency (<30 mL/min). Further, a significant portion of patients on dialysis pretransplant were reported to achieve subsequent dialysis independence.

Theoretically, the removal of nephrotoxic light chains with plasma exchange could avoid further renal failure and hopefully prevent irreversible renal failure. The Mayo Clinic group, in a small controlled trial, compared chemotherapy with chemotherapy plus plasma exchange and found only a trend in favor of the group treated with plasma exchange. Similarly, in a large randomized trial, there was no conclusive evidence that plasma exchange improved the outcome of patients with MM and acute renal failure, and decision-making should therefore be individualized. The use of high cut-off dialysis filters allows a higher rate of light-chain removal, but, despite this theoretical advantage, a randomized study did not show a benefit over conventional dialysis in a randomized clinical trial in patients with cast nephropathy. When excluding the patients who die soon after diagnosis, the median survival of patients with MM and nonreversible renal failure requiring chronic dialysis is almost 2 years, and 30% of them survive for more than 3 years. Thus, long-term dialysis is a worthwhile supportive measure for patients with MM and end-stage renal failure.

Spinal cord compression

Spinal cord compression from a plasmacytoma, which occurs in about 10% of patients, is the most frequent and serious neurological complication in MM. The thoracic spine is the most common site of involvement, followed by the lumbar region. The clinical picture of spinal cord compression consists of back pain and paraparesis. Although spinal cord compression can evolve for several days or even a few weeks, the onset can be abrupt, resulting in severe paraparesis or paraplegia in a few hours. Spinal cord compression is an emergency requiring immediate medical intervention, and when it is suspected,

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urgent MRI should be performed. If confirmed, treatment with high-dose dexamethasone must be started immediately. Simultaneous local radiation therapy should be started as soon as possible. If the spinal cord compression is caused by a vertebral collapse or by spinal instability rather than a plasmacytoma (which is very rare), urgent surgical decompression followed by fixation using a bone graft or methacrylate cement is required.

Infection

Infectious complications are a major cause of morbidity and mortality in patients with MM. The highest risk of infection is observed during the first 2 months of starting therapy, in patients with severe chemotherapy-induced granulocytopenia and in those with relapsed and refractory disease. The main causes of infection in MM include impaired antibody production, leading to a decrease in the uninvolved Igs, chemotherapy-induced granulocytopenia, renal function impairment, and glucocorticoid treatment, particularly with high-dose dexamethasone. Most infections in newly diagnosed patients and during the first cycles of chemotherapy are caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*; in patients with renal failure, as well as in those with relapsed and/or refractory advanced disease, >90% of the infectious episodes are caused by Gram-negative bacilli or *S. aureus*.

An infectious episode in a patient with MM should be managed as a potentially serious complication requiring immediate therapy. In case of suspected severe infection and before the identification of the causal agent, treatment for encapsulated bacteria and gram-negative microorganisms should be initiated. For patients with neutropenic fever related to chemotherapy, the use of G-CSF may be considered.

Although prophylaxis of infection in patients with MM is a controversial issue, some general guidelines can be provided. Intravenous Ig prophylaxis is not recommended, though it may be helpful in individuals with recurrent severe infections, despite antibiotic prophylaxis. Yearly influenza and pneumococcal vaccinations are recommended, particularly in patients with IgG myeloma with high serum M-protein levels, which are usually associated with very low levels of uninvolved Igs. The use of antibiotic prophylaxis is controversial, but it is likely of benefit within the first 2 months of initiation of therapy, especially in patients at high risk of infection (recent history of serious infections, such as recurrent pneumonia or renal failure). The TEAMM (Tackling Early Morbidity and Mortality in Myeloma) study randomized almost 1000 myeloma patients to receive either levofloxacin or placebo for 12 weeks following their diagnosis. Levofloxacin prophylaxis resulted in a significant reduction of events (fever or death) of 19% compared to 27% in the placebo arm with a hazard ratio of 1.52. Death from any cause within 12 weeks was observed in 8 patients in the levofloxacin group compared to 22 patients in the placebo group. Patients treated with proteasome inhibitors and monoclonal antibodies should receive prophylaxis against varicella-zoster virus infections.

Venous thromboembolism

Patients with MM have an increased risk of thrombosis, with a baseline risk of 3% to 4% of venous thrombotic events. This risk is significantly enhanced in the face of therapy, with higher risk associated with use of high-dose dexamethasone or cytotoxic chemotherapy, such as doxorubicin and immunomodulatory drugs. Other factors, such as reduced mobility due to neurological complications or bone pain, associated fractures, concurrent use of erythropoietic agents, and prior personal or family history of thrombotic events, all increase the risk of thromboembolic events. The current recommendations in patients with MM who are started on immunomodulatory agents is to use full-dose aspirin in the absence of risk factors for thrombosis and to use full-dose anticoagulation for those at higher risk.

Management of treatment-related toxicities

In addition to VTE that has been described previously, several common toxicities are encountered with the currently used antimyeloma agents. Hematological toxicity (myelosuppression) is the most common and is seen with nearly all the drugs, with the exception of corticosteroids and thalidomide. Neutropenia can be seen with nearly all classes of drugs, including the traditional cytotoxic drugs as well as lenalidomide and pomalidomide. The mechanism of neutropenia with immunomodulatory agents is believed to be a maturation blockade rather than inhibition of cell division as with traditional chemotherapy. Neutropenia should be managed through a combination of dose reduction and the use of growth factors, based on the general American Society of Clinical Oncology guidelines. Thrombocytopenia can also be seen with all these drugs, though thrombocytopenia may be more profound in the context of the PIs. The thrombocytopenia associated with PIs tends to be more transient and cyclic with rapid recovery following the initial effect of the drug. Lymphopenia can be seen with many of the

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drugs, especially steroids, but it typically does not need dose modifications. There is increased risk of infection, especially herpes zoster reactivation, with PIs and daratumumab, and infected patients should be treated prophylactically with acyclovir.

PN can be associated with many antimyeloma drugs, especially bortezomib and thalidomide. It is important to ask patients about neuropathy symptoms to identify PN early so that dose reductions can be instituted. In patients with painful neuropathy, the offending drug should be discontinued.

Gastrointestinal toxicity is also commonly encountered with many of the drugs. Diarrhea can accompany the use of bortezomib, carfilzomib, and panobinostat, and long-term use of lenalidomide. Bile acid malabsorption has been seen as a possible correlation to lenalidomide use and may offer an opportunity to use a bile acid sequestrant to mitigate chronic lenalidomide-induced diarrhea that is often seen. Constipation is a common side effect of thalidomide. Nausea can be seen with many of the drugs, especially the oral proteasome inhibitors. Patients should be managed symptomatically, and dose reduction should be pursued when feasible.

Other plasma cell disorders

Solitary plasmacytoma of bone

The existence of a solitary osseous plasmacytoma, usually involving the axial skeleton, has been recognized in up to 3% of patients with a PC neoplasm. The diagnostic criteria require a biopsy-proven solitary tumor of the bone with evidence of clonal plasma cells, absence of clonal PC infiltration in a bone marrow aspirate and biopsy sample, as well as no evidence of anemia, hypercalcemia, renal impairment, or myeloma-defining events. Furthermore, a skeletal survey, and either (PET)-CT or MRI of the spine and pelvis, must not show any additional lesions. With a thorough diagnostic evaluation and the use of advanced imaging, more patients are being diagnosed with MM and the diagnosis of a Solitary bone plasmacytoma is becoming rarer. The treatment of choice is local radiotherapy with 40 to 50 Gy in 1.8- to 2.0-Gy fractions. There are insufficient data to recommend the use of adjuvant chemotherapy or bisphosphonates. The rate of relapse or progression in patients who meet these criteria is estimated to be 10% over 3 years. Of note, approximately 40% of patients with solitary plasmacytoma of bone (SPB) are found to have up to 10% clonal bone marrow plasma cells which are characterized as SPB with minimal bone marrow involvement. This entity is treated like SPB, but the risk of progression is 60% over 3 years. Overall, about two thirds of patients with solitary bone plasmacytoma develop MM at 10 years' follow-up, with a median time to progression of 2 years. The risk of progression to overt myeloma is higher in patients in whom a monoclonal protein persists after eradication of the plasmacytoma with local treatment.

Solitary extramedullary plasmacytoma

Solitary extramedullary plasmacytomas are PC tumors that arise outside the bone marrow, most frequently in the upper respiratory tract (nose, paranasal sinuses, nasopharynx, and tonsils). Other sites include parathyroid gland, orbit, lung, spleen, gastrointestinal tract, testes, and skin. Diagnosis is based on the detection of the PC tumor in an extramedullary site, in the absence of clonal bone marrow PC infiltration, bone lytic lesions (confirmed by bone survey and either PET-CT or MRI of the spine and pelvis), and other signs of MM (end-organ damage). The treatment of choice for Solitary extramedullary plasmacytoma is local radiation therapy with 40 to 50 Gy in 1.8- to 2.0-Gy fractions. Adjuvant chemotherapy and bisphosphonates are not recommended. While local recurrence is very rare, up to 15% of patients eventually develop MM.

Nonsecretory MM

This specific type of MM requires particular attention because it is very difficult to diagnose. The only way to make a definitive diagnosis is to demonstrate the presence of tissue infiltration (usually of bone marrow) by cells with PC morphology. However, PC infiltration must be >10%, and clonality must be assessed by immunophenotyping (demonstration of cytoplasmic Igs with restricted light chain: positive production without excretion). However, exceptional cases exist in which no monoclonal protein can be observed within the PCs. In these cases, it is important to evaluate rarely identified heavy-chain isotypes such as IgD or IgE, and use PET/CT imaging and serial bone marrow biopsies as a means to diagnose and evaluate response to therapy.

Plasma cell leukemia

Plasma cell leukemia is a rare, aggressive form of MM characterized by high levels of PCs circulating in the peripheral blood. PCL can originate either as de novo (primary PCL) or as a secondary leukemic transformation of MM (secondary PCL) observed in 1% to 4% of all cases of MM. It was initially described by Robert Kyle in 1974 as blood plasmacytosis of more than 20% of total nucleated cells or an absolute number of circulating PCs of $>2 \times 10^9$/L.

The circulating PCs appear morphologically similar to the marrow PCs, though plasmablastic morphology

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is common, and these cells often lack CD56 expression, in contrast to more typical MM cells. From a cytogenetic standpoint, all abnormalities seen in MM can also be seen in PCL, but there appears to be a higher prevalence of monosomy 13, deletion 17p, and abnormalities in chromosome 1, in particular 1q21 amplification and del1p, abnormalities typically seen in higher proportion in relapsed myeloma.

Despite introduction of novel agents for MM, the outcomes of patients with PCL remains uniformly poor, with median OS of about 1 year. In patients with secondary PCL, the survival is even shorter. Modestly improved survival has been observed in recent years, as shown by an analysis of the SEER database of 445 patients with primary PCL diagnosed between 1973 and 2009, which reported median overall survival times of 5, 6, 4, and 12 months for those patients diagnosed during 1973-1995, 1996-2000, 2001-2005, and 2006-2009, respectively. There are no specific treatment approaches for PCL, but multidrug combinations including proteasome inhibitors, an immunomodulator, and potentially monoclonal antibodies appear to be a logical choice, along with the use of HDT/ASCT or allogeneic transplantation in eligible patients, followed by prolonged maintenance until progression.

Light-chain amyloidosis

Systemic amyloidosis represents a spectrum of disorders characterized by extracellular deposition of insoluble β pleated sheets of amyloid fibrils in various organs, leading to major organ dysfunction that can be fatal. Amyloid fibrils are identified by their characteristic appearance on electron microscopy and their affinity for Congo red. While over 40 proteins (eg, transthyretin [TTR]) have been described as potentially amyloidogenic, the most common form of amyloidosis, and the one that is the subject of this discussion, is the Ig light-chain amyloidosis, also called AL amyloidosis. AL amyloidosis is associated with a clonal B-cell proliferative disorder, most commonly a plasma cell dyscrasia or, less frequently, a subtype of lymphoma. Treatment with chemotherapy is given to suppress light-chain production by the underlying clonal process. It is therefore crucial to differentiate AL from other forms of amyloidosis which are not related to a malignancy and do not benefit from chemotherapy.

Epidemiology

AL amyloidosis is rare; the incidence is approximately 6 to 10 cases per million person-years. The median age at diagnosis is 64 years, and fewer than 5% of patients with AL amyloidosis are younger than 40 years. There is a slight male predominance with nearly 60% of patients being male. AL amyloidosis typically develops from the background of a plasma cell neoplasm but can be associated with other lymphoproliferative disorders in which there is excess secretion of κ or λ free light chains, including WM or chronic lymphocytic leukemia. Symptomatic myeloma, as defined by CRAB criteria, is diagnosed simultaneously in approximately 10% of patients with AL amyloidosis. In addition, up to 40% of patients with AL amyloidosis have 10% or more bone marrow plasma cells at diagnosis but do not meet CRAB criteria. Later progression to overt myeloma in patients with isolated AL amyloidosis is rare. In a series of 1596 patients with AL amyloidosis seen at the Mayo Clinic, only 6 (0.4 %) developed MM.

Clinical presentation

The clinical presentation is dictated by the spectrum and severity of the organ involvement and can be varied with nonspecific symptoms. The common presentations, based on the organ system involved, are detailed in Table 25-14. The 10% of AL patients with coexisting symptomatic MM may present with signs and symptoms related to myeloma CRAB criteria.

Diagnosis and staging

Diagnosis of AL amyloidosis requires histologic confirmation of the presence of amyloid deposition in any body tissue and proof that this amyloid arises from clonal Ig light chains by amyloid subtyping. In addition, identification of a monoclonal protein in the serum or urine and serum free light-chain assay results provide supportive information for the diagnosis and a measure to follow disease response. A bone marrow examination allows classification of the primary disorder, which, in the majority of patients, would be classified as MGUS, if not for the presence of amyloid formation.

Detecting amyloid deposition

The typical sites for demonstrating amyloid deposits are the organs involved or surrogate sites, such as the bone marrow and abdominal subcutaneous fat. A combination of fat aspirate and a marrow biopsy is preferred because patients typically would undergo a bone marrow examination for their underlying monoclonal gammopathy; a fat aspirate can be performed conveniently at the same time. Either or both are positive in 90% of patients with AL amyloidosis. If these sites are negative for amyloid, a biopsy directed at the affected organ should be performed. On hematoxylin- and eosin-stained biopsy sections, amyloid appears as a pink, amorphous, waxy substance, but it binds strongly to Congo red (ie, it is Congophilic,

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Table 25-14 Spectrum of organ involvement and clinical features in AL amyloidosis

Organ	Clinical features
Kidney	Involved in ~70% of patients
	Typically presents as nephrotic range proteinuria; renal failure at diagnosis uncommon
	Edema, hyperlipidemia
Heart	Involvement seen in approximately 60% of patients
	Typically presents with increased thickness of interventricular septum and ventricular wall; restrictive cardiomyopathy or conduction disturbances, arrhythmias, rarely with angina due to vascular involvement; N-terminal serum brain natriuretic peptide (NT-proBNP) and troponin are markers of cardiac involvement
	Dyspnea on exertion, orthopnea, syncope, edema, fatigue, sudden cardiac death, signs of congestive heart failure
Liver	Hepatic involvement can be seen in up to 60% of patients
	Presents with hepatomegaly and elevated liver tests, especially elevated alkaline phosphatase and bilirubin; frank hepatic failure uncommon
	Hepatomegaly, weight loss, fatigue, jaundice
Nervous system	Typically affects peripheral nerves (20%), sensory more than motor or autonomic nerves (15%)
	Numbness, paresthesia, and pain due to peripheral nerve involvement; postural hypotension, bladder and bowel dysfunction, related to autonomic neuropathy
Gastrointestinal tract	Approximately 30% of patients
	Bleeding, diarrhea, weight loss, gastroparesis, constipation, bacterial overgrowth, malabsorption, and intestinal pseudo-obstruction resulting from dysmotility
Soft tissue and muscle	Involved in nearly one third of patients
	Macroglossia, proximal muscle weakness, arthropathy, carpal tunnel syndrome
Coagulation system	Increased bleeding or skin purpura related to vascular friability, altered coagulation profile with acquired factor X deficiency due to binding to amyloid fibrils in the spleen and liver, decreased synthesis of coagulation factors in patients with advanced liver disease; and acquired von Willebrand disease

imparting a green birefringence under polarized light) and to thioflavine-T, producing an intense yellow-green fluorescence. The presence of amyloid can also be confirmed by its characteristic appearance on electron microscopy.

Amyloid subtyping to identify amyloid type

Monoclonal gammopathies are common especially in older patients, and the detection of an M protein in a patient with amyloidosis does not necessarily establish a diagnosis of AL amyloid because a patient may, for example, have transthyretin amyloidosis and an unrelated MGUS. Traditionally, the identification of the protein origin of the amyloid fibrils has utilized immunohistochemistry or immunofluorescence (eg, for κ and λ light chains, transthyretin, and serum amyloid A). However, this method can lead to false-positive and false-negative results. It is important to realize that over 30 different proteins have been identified that can lead to amyloid deposits. Laser microdissection, selecting tissue for mass spectrometry, can be used to determine the specific type of amyloid deposited. This technique can identify the amyloid type with over 98% specificity and sensitivity and is therefore the preferred method for amyloid subtyping.

Detecting and quantifying the monoclonal process

The PC proliferation in AL amyloidosis is typically low burden, with <10% PCs in over half of the patients. Serum and/or urine protein electrophoresis with immunofixation can identify a monoclonal protein in nearly 90% of patients with AL amyloidosis. Addition of the serum free light-chain assay to the diagnostic workup increases the yield to over 98% of the patients. Most patients with AL amyloidosis have little or no intact monoclonal Ig but are characterized by the presence of monoclonal free light chain. The monoclonal light-chain type is λ in approximately 70% of cases, κ in 25%, and biclonal in 5%.

Clinical evaluation and disease staging

In addition to a detailed history and physical examination, including orthostatic blood pressure and neurologic examinations; laboratory studies should be performed including a complete blood count with differential, chemistries with liver and renal function and electrolytes, coagulation screening studies including prothrombin time, partial thromboplastin time, serum and urine protein electrophoresis with immunofixation, serum free light-chain assay, 24-hour urinary protein measurement, assessment

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of creatinine clearance, and NT-proBNP, troponin T, and thyroid-stimulating hormone. Detailed coagulation testing or screening tests should be considered for those with abnormal bleeding. A bone marrow aspirate and biopsy with a myeloma FISH panel along with a fat aspirate should be done as discussed previously for assessment of PCs, as well as for amyloid detection and identification. Bone imaging is used to assess for myeloma bone lesions. Electrocardiogram and echocardiogram should be performed to look for cardiac involvement. MRI can provide helpful information if an echocardiogram is nondiagnostic and suspicion of cardiac involvement is high. Ultrasound or CT may be used to assess craniocaudal liver size. Patients with neurologic symptoms should have electromyography and nerve conduction studies for diagnosis as well as baseline assessment for future response determination. Gastric-emptying studies may be of benefit in patients with upper gastrointestinal symptoms. Additional evaluation should be determined based on suspected organ involvement.

The prognosis of AL amyloidosis varies considerably depending on the number and extent of organ involvement. The overall outcome, while getting slightly better with time, still remains poor with over 40% of patients dying within 1 year of diagnosis, predominantly from heart failure. Though multiple prognostic models have been proposed for patients with amyloidosis, models that incorporate markers of cardiac damage have high predictive value for early death in AL amyloidosis. The revised Mayo Clinic Amyloid Staging system classifies patients as having stage I, II, III, or IV disease based upon the identification of 0, 1, 2, or 3 of the following risk factors: NT-pro-BNP ≥1800 ng/L, cardiac troponin T ≥0.025 μg/L, and a difference between involved and uninvolved serum free light chains ≥18 mg/dL. Median overall survivals from diagnosis for stages I-IV were 94, 40, 14, and 6 months, respectively.

Treatment approaches

The overall goal of traditional AL amyloidosis treatment is the reduction of circulating clonal light chains to decrease amyloid deposition, limit additional organ damage, and potentially enable degradation of existing amyloid deposits. Treatment approaches in AL amyloidosis have closely paralleled the developments in the field of MM. While the specific drugs that are currently employed reflect their use in PC disorders, The 3 most common approaches in AL amyloidosis consist of HDT and autologous stem cell transplantation, melphalan and dexamethasone, and bortezomib-based combinations. Most recently the combination of daratumumab plus CyBORD (ANDROMEDA) improves survival for patients with AL. Whether SCT is still needed in a patient who undergoes induction therapy and achieves a sCR or an otherwise deep response remains a topic of controversy (see the following).

Response assessment

There are critical differences between response assessments in AL amyloidosis (Table 25-15) and MM because response assessment in AL amyloidosis needs to capture both the hematologic response as well as any improvements in organ function, the latter being more important from a patient-outcome standpoint. Given that many patients with AL amyloidosis do not have measurable levels of intact immunoglobulin M protein, the serum free light-chain assay has become the marker of choice for following the effect of treatments on the clonal PCs. However, the ultimate goal of therapy in AL amyloidosis is to reverse organ dysfunction. Multiple studies have demonstrated a close relationship between hematological response and organ response, with deep responses (VGPR or better) being associated with a higher rate of organ response.

Initial treatment of AL amyloidosis

The initial approach to treatment of AL amyloidosis depends to a great extent on the patient's eligibility for HDT/ASCT. Initial experience with HDT in amyloidosis was beset with high treatment-related mortality resulting primarily from cardiac adverse events. Incorporation of standard prognostic factors into transplantation-eligibility criteria has greatly reduced the mortality associated with this procedure. Currently, patients with a physiologic age of 70 years or older and with a troponin T <0.06 ng/mL, NT-proBNP <5000 ng/L, ECOG performance status ≤2, New York Heart Association functional status class I or II, systolic blood pressure >90 mm Hg, creatinine clearance >30 mL/min, and no more than 2 organs significantly involved (liver, heart, kidney, or autonomic nerve) can be considered for HDT. The decision to proceed should follow a careful discussion with the patient with respect to the potential toxicities and anticipated outcomes given that limited organ reserve, due to amyloid involvement, presents an increased risk for treatment-related toxicity and mortality. The support for HDT is based largely on single-institution studies demonstrating an improved outcome among patients who proceeded to HDT compared with those who, though eligible, did not proceed to HDT. In addition, single-center data as well as data from the CIBMTR suggest that patients undergoing HDT have high rates of hematological responses as well as organ responses and a high median progression-free survival measured in years. In contrast, a randomized French trial

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Table 25-15 Criteria for assessment of treatment response in AL amyloidosis

Hematologic or organ response	Description of response
Hematologic response	
Complete response	Normalization of the FLC levels and ratio, negative serum and urine immunofixation
Very good partial response	Reduction in the difference between involved FLC and uninvolved FLC (dFLC) to <40 mg/L
Partial response	≥50% reduction in dFLC
No response progression	Less than a PR
	Free light-chain increase of 50% to ≥100 mg/L. If patient achieved a CR previously, any detectable M protein or abnormal FLC ratio (light chain must double). If patient achieved a PR previously, 50% increase in serum M protein to ≥0.5 g/dL or 50% increase in urine M protein to ≥200 mg/day (a visible peak must be present).
Organ response	
Cardiac	Response: NT-proBNP response (≥30% and ≥300 ng/L decrease in patients with baseline NT-proBNP
	≥650 ng/L) or NYHA class response (2 class decrease in subjects with baseline NYHA class 3 or 4)
	Progression: NT-proBNP progression (>30% and >300 ng/L increase) or cardiac troponin progression (≥33% increase) or ejection fraction progression (≥10% decrease)
Kidney	Response: ≥30% decrease in proteinuria or drop of proteinuria below 0.5 g/24 hours in the absence of renal progression
	Progression: ≥25% decrease in eGFR
Liver	Response: 50% decrease in abnormal alkaline phosphatase value; decrease in liver size radiologically of at least 2 cm
	Progression: 50% increase of alkaline phosphatase above the lowest value
Peripheral nervous system	Response: improvement in electromyogram nerve conduction velocity
	Progression: progressive neuropathy by electromyography or nerve conduction velocity

demonstrated better overall survival outcomes with oral chemotherapy compared with HDT.

Patients frequently undergo stem cell mobilization and transplantation as their initial therapy, though induction therapy with a bortezomib-based regimen can be used. The most commonly used conditioning regimen in AL amyloidosis remains melphalan, 200 mg/m^2, given over 2 days. In patients with renal dysfunction and in those with a poorer performance status, a risk-adapted strategy of reducing the melphalan dose has been tried, but studies suggest that dose reduction of melphalan may be associated with an inferior outcome. In the Mayo series of 454 patients, 100-day mortality was 9%. A partial response or better was seen in 80%, including 40% with a CR. The median overall survival was 113 months with estimated rates of survival at 1 and 5 years of 87% and 66%, respectively. Estimated 5-year survival rates for those attaining a hematologic CR, VGPR, PR, and less than a PR were 90%, 74%, 56%, and 35%, respectively. Similar results were seen in a Boston University series, with a 100-day mortality of 7.5% and a median overall survival of 7.6 years. CR was seen in 40% and that translated into a superior overall survival (not reached versus 6.3 years). Organ responses were observed in 79% of patients achieving a hematologic CR compared to 39% in patients who did not achieve a CR.

Recent studies have suggested a response and risk-adapted strategy of using post-SCT consolidation in patients who fail to achieve a deep response with the SCT. In a phase 2 study of 40 patients, those who did not achieve a hematologic CR after SCT received 6 cycles of bortezomib and dexamethasone. With this approach, the estimated 2-year OS was 82%. These initial results appear promising, and this approach is being studied further.

Bortezomib-based regimens

Given the efficacy of bortezomib in MM, there has been significant interest in examining its role in patients with AL amyloidosis. In a large European study of 230 newly diagnosed patients treated with cyclophosphamide, bortezomib, and dexamethasone, the overall hematologic response rate was 60% including a 23% CR rate. Organ responses of the heart and kidneys were seen in 17% and 25%, respectively. The median time to next therapy was 13 months, and overall survival at 3 years was 55%. A subsequent randomized study compared the combination of

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melphalan-dexamethasone to melphalan-dexamethasone plus bortezomib in 110 newly diagnosed patients with amyloidosis. The addition of bortezomib improved overall response rates from 56% to 81% and the VGPR/CR rate from 38% to 64%. While the rate of renal-organ improvement was the same in both arms (48%), more patients in the bortezomib arm achieved a cardiac response (38% compared to 24%). Bortezomib has also been studied in combination with dexamethasone in a nonrandomized phase 2 trial of bortezomib administered either once weekly (1.6 mg/m^2 on days 1, 8, 15, and 22 of 35-day cycles) or twice weekly (1.3 mg/m^2 on days 1, 4, 8, and 11 of 21-day cycles). Seventy patients with relapsed AL amyloidosis were treated; the hematologic response rate was 69% and included 38% CRs. Estimated median overall survival was 62 months. The twice-weekly regimens had a similar response rate but were associated with higher rates of adverse events. Studies with other proteasome inhibitors including ixazomib and carfilzomib are ongoing.

Immunomodulator-based regimens

Thalidomide, lenalidomide, and pomalidomide have been studied in AL amyloidosis, either with dexamethasone or in combination with melphalan or cyclophosphamide. The hematological response rates range from 50% to 80%, with up to half of the patients achieving an organ response. Immunomodulatory agents are not as well tolerated as they are in the setting of myeloma; lower doses appear to mitigate this problem to some extent. Immunomodulator therapy has been associated with more toxicity among the patients with significant heart disease. Examination of the laboratory tests of patients receiving Immunomodulators clearly show an increase in NT-proBNP levels which may be accompanied by worsening cardiac function, which can be asymptomatic.

Monoclonal antibodies

While monoclonal antibodies are commonly used in myeloma, there has been limited experience using monoclonal antibodies in patients with AL amyloidosis. Subcutaneous daratumumab has recently been approved for its use in combination with cyclophosphamide, bortezomib, and dexamethasone for the treatment of AL amyloidosis. The ANDROMEDA study randomized patients to receive the triplet combination with or without daratumumab. Patients receive 6 cycles of quadruplet therapy followed by continuous monthly daratumumab for up to 24 cycles. The quadruplet regimen resulted in higher ORR (92% versus 77%) and improved hematologic complete responses (42% versus 13%). The combination had an acceptable safety profile, consistent with that previously observed for each of the agents alone. In addition to plasma cell–directed immunotherapy, several novel experimental antibodies targeting the amyloid protein are currently under clinical investigation.

Waldenström macroglobulinemia

Waldenström macroglobulinemia (WM) is a rare disorder characterized by the presence of a monoclonal IgM gammopathy in the blood and clonal lymphoplasmacytic cells in the bone marrow. The incidence is approximately 3 per million people per year, with 1400 new cases diagnosed in the United States each year. The median age at diagnosis is 64 years, with a gender distribution similar to other PC disorders, approximately 60% male. In contrast to MM, WM is much more common in individuals of European descent than in other ethnic groups.

The etiology of WM is unknown, though association with infections and exposure to pesticides suggests an environmental impact. A familial predisposition is observed in up to 20% of patients. A recurrent mutation of the *MYD88* gene (MYD88 L265P) is present in >90% of patients with WM, though this finding is not specific to WM and can be seen in other B-cell neoplasms. In addition, 40% of patients have a recurrent mutation in the CXCR4 gene. The pattern of somatic mutations suggests development at a late stage of B-cell differentiation, a post–germinal center IgM memory B cell that has undergone somatic hypermutation but has failed to undergo isotype class switching.

The clinical presentation of WM is tied to the presence of the IgM monoclonal protein in the blood (symptoms secondary to hyperviscosity, cryoglobulinemia, bleeding disorders, autoimmune hemolytic anemia), marrow or tissue infiltration by the lymphoplasmacytic cells (anemia, hepatosplenomegaly, lymphadenopathy), or autoimmune phenomena driven by the monoclonal protein (neuropathy). Most patients with WM present with nonspecific constitutional symptoms, and some of the patients may be asymptomatic at diagnosis. The most common presenting features include weakness, fatigue, weight loss, and oozing of blood from the nose or gums. Recurrent infections may occur due to a decrease in other unaffected Igs.

To make a diagnosis of WM, an IgM monoclonal protein of any size must be present in the serum, with 10% or more infiltration of the bone marrow by small lymphocytes that exhibit lymphoplasmacytic features and express a typical immunophenotype: surface IgM$^+$, CD5$^{+/-}$, CD10$^-$, CD19$^+$, CD20$^+$, CD22$^+$, CD23$^-$, CD25$^+$, CD27$^+$, FMC7$^+$, CD103$^-$, CD138$^-$. The PC component may be CD138$^+$, CD38$^+$, and CD45$^-$ or CD45^{dim}. The phenotypic pattern is of critical importance in excluding

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other conditions, including chronic lymphocytic leukemia, marginal-zone and mantle-cell lymphoma. In addition, the MYD 88 mutation can be valuable in differentiating WM from other conditions. An additional small subset of patients harbor mutations of CXCR4 which can be overlapping with MYD88 mutations and are associated with a more aggressive phenotype.

It is important to distinguish symptomatic disease from early or precursor forms, such as IgM MGUS or smoldering WM. IgM MGUS is characterized by serum IgM concentration <3.0 g/dL, absence of anemia, hepatosplenomegaly, lymphadenopathy, systemic symptoms, and minimal (<10%) or no lymphoplasmacytic infiltration of the bone marrow. Patients who meet the criteria for WM, but who have no clinical symptoms or anemia, hepatosplenomegaly, lymphadenopathy, or hyperviscosity, are considered to have smoldering WM. In patients with IgM monoclonal gammopathy, especially of the κ subtype, and urticaria, the diagnosis of Schnitzler syndrome should be considered. Additional symptoms may include fever, bone pain, and arthralgia. There is no single diagnostic test, but patients may have dramatic responses to therapy with IL-1 receptor antagonists.

IgM MM is quite rare, comprising only 0.5% of a large Mayo Clinic series. Pathological distinction based on marrow appearance can be difficult in some instances, and clinical presentation may be relied on to correctly classify these patients. Presence of lytic bone lesions clearly suggests the presence of MM pathology rather than the pathology typical of WM. In contrast, symptoms of hyperviscosity and the presence of lymphadenopathy or splenomegaly favor a diagnosis of WM. Other features that may help with making the diagnosis includes the presence of typical chromosomal abnormalities, such as the IgH translocations seen in MM.

Treatment approaches

Many patients with WM are asymptomatic; these patients can be observed until they develop symptoms without compromising their long-term outcomes. Indications for treatment include systemic symptoms (fever, night sweats, fatigue, weight loss), along with physical findings (symptomatic lymphadenopathy, hepatomegaly, and/or splenomegaly), and cytopenias (anemia, thrombocytopenia, neutropenia). Hyperviscosity can lead to a variety of symptoms, including mucosal bleeding, blurred vision, headaches, dizziness, paresthesias, retinal-vein engorgement and flame-shaped hemorrhages, papilledema, and neurologic impairment, all of which point to the need for therapy. In addition, paraneoplastic neuropathy and symptoms related to associated conditions (cryoglobulinemia, cold agglutinin, hemolytic anemia, amyloidosis) may represent treatment indications.

The initial management of patients with symptomatic WM depends on the age and the potential for HDT and ASCT, functional status, presence and severity of symptoms, especially hyperviscosity-related symptoms, and presence of other comorbidities. Patients who can be future candidates for autologous hematopoietic cell transplant should avoid treatment with agents that might interfere with stem cell collection (alkylators except for cyclophosphamide and purine nucleoside analogs).

Patients with symptoms of hyperviscosity require emergent plasmapheresis in addition to specific systemic therapy for WM. The large size of the IgM molecule allows rapid removal using plasmapheresis, resulting in rapid symptomatic improvement. Red blood cell transfusions should be avoided, if possible, prior to plasmapheresis, because they might further increase serum viscosity. Along with plasmapheresis, systemic therapy should be started.

Rituximab, an anti-CD20 monoclonal antibody, is an important component of the current treatment regimens for WM. Patients with mild symptoms and no urgent requirement for intervention can be considered for single-agent rituximab therapy. While rituximab is well tolerated and can be safely combined with a variety of other drugs, transient increases in serum IgM levels (IgM flare) and associated hyperviscosity may occur after the administration of rituximab and can lead to clinical consequences; therefore, careful short-term follow-up is recommended. The overall response rate for single-agent rituximab is approximately 50%.

In the vast majority of patients, rituximab should be combined with other chemotherapy agents. The most commonly used regimens include dexamethasone, rituximab, cyclophosphamide (DRC), bortezomib plus rituximab with or without dexamethasone, and bendamustine plus rituximab. Overall response rates of 60% to 90% have been observed with these regimens. Of note, the time-to-response for DRC is relatively long at 4.1 months; other regimens should be considered if a more rapid disease response is desired.

Ibrutinib, a small-molecule inhibitor of Bruton tyrosine kinase, has considerable efficacy in WM. In a phase 2 study of 63 patients with symptomatic WM, who had received at least one prior treatment, the overall response rate was 90.1% when treated with daily ibrutinib. Responses were rapid, with a median time-to-response of 4 weeks which was highest in the subgroup of patients with MYD88 L265P/CXCR4WT. Toxicity was very manageable, with hematologic toxicities being the most common.

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The phase 3 iNNOVATE trial compared newly diagnosed and patients with relapsed/refractory WM treated with ibrutinib/rituximab or rituximab plus placebo. At 30 months of follow-up the combination arm showed an ORR of 95% compared with 48% in the placebo-controlled arm. In newly diagnosed patients, the combination approach showed an improved PFS at 30 months (79%) compared to rituximab (41%).

Nucleoside analogs, such as fludarabine or cladribine, have significant activity in WM and have been used in combination with rituximab in regimens such as cladribine and rituximab, fludarabine and rituximab, and fludarabine, cyclophosphamide and rituximab. However, use of this class of drugs have been associated with stem cell toxicity with subsequent myelodysplasia diagnosis as well as increased risk of transformation to high-grade lymphoma. The predominant short-term toxicities with nucleoside-analog-containing regimens are myelosuppression and immunosuppression.

Other agents that are currently being investigated for WM include proteasome inhibitors (carfilzomib and ixazomib), anti-CD20 antibodies (ofatumumab and obinotuzumab), CXCR 4 antagonists, venetoclax and MTOR inhibitors.

Given the rarity of the disease, there is limited experience with HDT and SCT in WM. A retrospective analysis of 158 patients with WM who underwent transplantation in Europe showed a nonrelapse mortality of 3.8% at 1 year. The development of a second malignancy was reported in 8.4% of patients by 5 years. Progression-free survival and overall survival at 5 years were 40% and 66%, respectively.

POEMS syndrome

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome (also known as osteosclerotic myeloma, Crow-Fukase syndrome, or Takatsuki syndrome) is characterized by the presence of a monoclonal PC disorder, PN, and 1 or more of the following features: osteosclerotic myeloma, Castleman disease (angiofollicular lymph node hyperplasia), increased levels of serum vascular endothelial growth factor, organomegaly, endocrinopathy, edema, typical skin changes, and papilledema (Table 25-16).

The cause of POEMS syndrome is unknown, although overproduction of proinflammatory and other cytokines, like vascular endothelial growth factor and IL-6, have been implicated in the symptomatology seen in this disorder. It is believed that stromal cells produce these cytokines in response to the clonal PC population.

The incidence of this disorder is unknown. In a Mayo Clinic series of 99 patients with POEMS syndrome, the median age was 51 years and 63% were males. Patients may present with a constellation of symptoms and this often makes the diagnosis difficult. In addition to the obligate polyneuropathy and monoclonal protein with associated PC disorder, nearly all patients have osteosclerotic bone lesions, and more than half have organomegaly, skin changes, and endocrinopathy. Other manifestations include weight loss, fatigue, papilledema, edema, ascites, and pleural effusion. PN is usually the predominant clinical feature and typically begins as a distal, symmetric sensory neuropathy, including tingling and paresthesias, which frequently progresses to

Table 25-16 Mayo Clinic criteria for the diagnosis of POEMS syndrome

Both of the following mandatory criteria must be present:
Polyneuropathy
Monoclonal PC proliferative disorder
Plus at least 1 additional major criterion:
Osteosclerotic or mixed sclerotic/lytic lesion visualized on plain films or computed tomography measuring at least 0.8 cm in the longest dimension
Castleman disease
Elevated serum or plasma vascular endothelial growth factor levels at least 3 to 4 times the upper limit of normal
Plus at least 1 minor criterion:
Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
Extravascular volume overload (peripheral edema, ascites, or pleural effusion)
Endocrinopathy (excluding diabetes mellitus or hypothyroidism)
Skin changes
Papilledema
Thrombocytosis or polycythemia

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include motor innervation leading to a predominantly motor chronic inflammatory demyelinating polyneuropathy. Unlike AL amyloidosis, autonomic neuropathy is not observed in POEMS syndrome. The presence of a monoclonal PC disorder is required for a diagnosis of POEMS syndrome. In the Mayo Clinic series, 88% of patients had a monoclonal protein in the serum and/or urine; for the remaining patients, a clonal PC disorder was confirmed by immunohistochemistry of a biopsy specimen. The type of light chain seen in POEMS syndrome is almost always λ.

Treatment

In patients with 1 to 3 isolated bone lesions and no evidence of bone marrow involvement, limited field radiation at a dose of 40 to 50 Gy is the preferred treatment modality. In a retrospective study from the Mayo Clinic, radiation therapy to the lesions resulted in hematologic response (complete or partial), VEGF response, FDG-PET response, and clinical responses of 31%, 14%, 22%, and 47%, respectively. Improvements were seen in PN, anasarca, organomegaly, papilledema, skin changes, serum M-spikes, and plasma VEGF levels. The estimated overall and event-free survivals at 4 years were 97% and 5%, respectively.

Systemic chemotherapy should be considered for patients with widespread osteosclerotic lesions or bone marrow involvement. Many of the drugs used for myeloma treatment, including melphalan and steroid combinations, bortezomib, thalidomide, and lenalidomide, have been used for treatment of bone lesions with varying degrees of success. Anecdotal reports suggest a role for agents with anti-cytokine/anti-VEGF activity in ameliorating some of the signs and symptoms of this disorder. In young patients who require systemic therapy, HDT followed by autologous stem cell transplantation has been shown to be of benefit. In a large series reported by the Mayo Clinic, clinical improvement was seen in nearly all patients. While neurologic symptoms often take several years to improve fully, other symptoms tend to respond rapidly following HDT. At a median follow-up of 45 months, 5-year overall and progression-free survival rates were 94% and 75%, respectively.

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